

DF

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification⁶ : C07K 5/078, A61K 38/05</p>	<p>A1</p>	<p>(11) International Publication Number: WO 99/06437 (43) International Publication Date: 11 February 1999 (11.02.99)</p>
<p>(21) International Application Number: PCT/US98/16070 (22) International Filing Date: 31 July 1998 (31.07.98) (30) Priority Data: 08/904,423 31 July 1997 (31.07.97) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 08/904,423 (CIP) Filed on 31 July 1997 (31.07.97) (71) Applicants (for all designated States except US): ATHENA NEUROSCIENCES, INC. [US/US]; 800 Gateway Boulevard, South San Francisco, CA 94080 (US). AMERICAN HOME PRODUCTS CORPORATION [US/US]; 5 Giraldi Farms, Madison, NJ 07940 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): THORSETT, Eugene, D. [US/US]; 571 Buena Vista, Moss Beach, CA 94038 (US). SEMKO, Christopher, M. [CA/US]; 2361 Carpenter Court, Fremont, CA 94539 (US). PLEISS, Michael, A. [US/US]; 848 Stella Court, Sunnyvale, CA 94087 (US). KREFT, Anthony [US/US]; 43 Barley Court, Langhorne, PA 19047</p>	<p>(US). KONRADI, Andrei, W. [US/US]; 95 Cervantes #105, San Francisco, CA 94123 (US). GRANT, Francine, S. [FR/US]; 3735 Sacramento Street, San Francisco, CA 94118 (US). BAUDY, Reinhardt, Bernhard [DE/US]; 5281 Harrington Court, Doylestown, PA 18901 (US). SARANTAKIS, Dimitrios [US/US]; 262 Sentinel Avenue, Newtown, PA 18940 (US). (74) Agents: SWISS, Gerald, F. et al.; Burns, Doane, Swecker & Mathis, L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>	
<p>(54) Title: SULFONYLATED DIPEPTIDE COMPOUNDS WHICH INHIBIT LEUKOCYTE ADHESION MEDIATED BY VLA-4</p>		
<p>(57) Abstract</p> <p>Disclosed are compounds which bind VLA-4. Certain of these compounds also inhibit leukocyte adhesion and, in particular, leukocyte adhesion mediated by VLA-4. Such compounds are useful in the treatment of inflammatory diseases in a mammalian patient, e.g., human, such as asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, rheumatoid arthritis, tissue transplantation, tumor metastasis and myocardial ischemia. The compounds can also be administered for the treatment of inflammatory brain diseases such as multiple sclerosis.</p>		

5

SULFONYLATED DIPEPTIDE COMPOUNDS WHICH INHIBIT
LEUKOCYTE ADHESION MEDIATED BY VLA-4

10

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to compounds which inhibit leukocyte adhesion
and, in particular, leukocyte adhesion mediated by VLA-4.

15

References

The following publications, patents and patent applications are cited
in this application as superscript numbers:

20

¹ Hemler and Takada, *European Patent Application Publication*
No. 330,506, published August 30, 1989

² Elices, et al., *Cell*, 60:577-584 (1990)

25

³ Springer, *Nature*, 346:425-434 (1990)

⁴ Osborn, *Cell*, 62:3-6 (1990)

⁵ Vedder, et al., *Surgery*, 106:509 (1989)

30

⁶ Pretolani, et al., *J. Exp. Med.*, 180:795 (1994)

⁷ Abraham, et al., *J. Clin. Invest.*, 93:776 (1994)

35

⁸ Mulligan, et al., *J. Immunology*, 150:2407 (1993)

- 9 Cybulsky, et al., *Science*, 251:788 (1991)
- 10 Li, et al., *Arterioscler. Thromb.*, 13:197 (1993)
- 5 11 Sasseville, et al., *Am. J. Path.*, 144:27 (1994)
- 12 Yang, et al., *Proc. Nat. Acad. Science (USA)*, 90:10494 (1993)
- 10 13 Burkly, et al., *Diabetes*, 43:529 (1994)
- 14 Baron, et al., *J. Clin. Invest.*, 93:1700 (1994)
- 15 15 Hamann, et al., *J. Immunology*, 152:3238 (1994)
- 16 Yednock, et al., *Nature*, 356:63 (1992)
- 17 Baron, et al., *J. Exp. Med.*, 177:57 (1993)
- 20 18 van Dinther-Janssen, et al., *J. Immunology*, 147:4207 (1991)
- 19 van Dinther-Janssen, et al., *Annals. Rheumatic Dis.*, 52:672 (1993)
- 25 20 Elices, et al., *J. Clin. Invest.*, 93:405 (1994)
- 21 Postigo, et al., *J. Clin. Invest.*, 89:1445 (1991)
- 22 Paul, et al., *Transpl. Proceed.*, 25:813 (1993)
- 30 23 Okarhara, et al., *Can. Res.*, 54:3233 (1994)
- 24 Paavonen, et al., *Int. J. Can.*, 58:298 (1994)
- 35 25 Schadendorf, et al., *J. Path.*, 170:429 (1993)
- 26 Bao, et al., *Diff.*, 52:239 (1993)
- 27 Lauri, et al., *British J. Cancer*, 68:862 (1993)
- 40 28 Kawaguchi, et al., *Japanese J. Cancer Res.*, 83:1304 (1992)
- 29 Kogan, et al., *U.S. Patent No. 5,510,332*, issued April 23, 1996
- 45 30 International Patent Appl. Publication No. WO 96/01644

All of the above publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

State of the Art

VLA-4 (also referred to as $\alpha_4\beta_1$ integrin and CD49d/CD29), first identified by Hemler and Takada¹ is a member of the β_1 integrin family of cell surface receptors, each of which comprises two subunits, an α chain and a β chain. VLA-4 contains an α_4 chain and a β_1 chain. There are at least nine β_1 integrins, all sharing the same β_1 chain and each having a distinct α chain. These nine receptors all bind a different complement of the various cell matrix molecules, such as fibronectin, laminin, and collagen. VLA-4, for example, binds to fibronectin. VLA-4 also binds non-matrix molecules that are expressed by endothelial and other cells. These non-matrix molecules include VCAM-1, which is expressed on cytokine-activated human umbilical vein endothelial cells in culture. Distinct epitopes of VLA-4 are responsible for the fibronectin and VCAM-1 binding activities and each activity has been shown to be inhibited independently.²

Intercellular adhesion mediated by VLA-4 and other cell surface receptors is associated with a number of inflammatory responses. At the site of an injury or other inflammatory stimulus, activated vascular endothelial cells express molecules that are adhesive for leukocytes. The mechanics of leukocyte adhesion to endothelial cells involves, in part, the recognition and binding of cell surface receptors on leukocytes to the corresponding cell surface molecules on endothelial cells. Once bound, the leukocytes migrate across the blood vessel wall to enter the injured site and release chemical mediators to combat infection. For reviews of adhesion receptors of the immune system, *see*, for example, Springer³ and Osborn⁴.

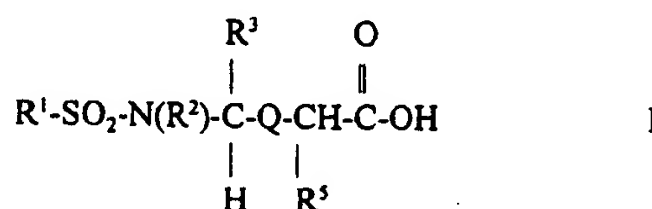
Inflammatory brain disorders, such as experimental autoimmune encephalomyelitis (EAE), multiple sclerosis (MS) and meningitis, are examples of central nervous system disorders in which the endothelium/leukocyte adhesion mechanism results in destruction to otherwise healthy brain tissue. Large numbers of leukocytes migrate across the blood brain barrier (BBB) in subjects with these inflammatory diseases. The leukocytes release toxic mediators that cause extensive tissue damage resulting in impaired nerve conduction and paralysis.

In other organ systems, tissue damage also occurs via an adhesion mechanism resulting in migration or activation of leukocytes. For example, it has been shown that the initial insult following myocardial ischemia to heart tissue can be further complicated by leukocyte entry to the injured tissue causing still further insult (Vedder et al.⁵). Other inflammatory conditions mediated by an adhesion mechanism include, by way of example, asthma⁶⁻⁸, Alzheimer's disease, atherosclerosis⁹⁻¹⁰, AIDS dementia¹¹, diabetes¹²⁻¹⁴ (including acute juvenile onset diabetes), inflammatory bowel disease¹⁵ (including ulcerative colitis and Crohn's disease), multiple sclerosis¹⁶⁻¹⁷, rheumatoid arthritis¹⁸⁻²¹, tissue transplantation²², tumor metastasis²³⁻²⁸, meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

In view of the above, assays for determining the VLA-4 level in a biological sample containing VLA-4 would be useful, for example, to diagnosis VLA-4 mediated conditions. Additionally, despite these advances in the understanding of leukocyte adhesion, the art has only recently addressed the use of inhibitors of adhesion in the treatment of inflammatory brain diseases and other inflammatory conditions^{29,30}. The present invention addresses these and other needs.

SUMMARY OF THE INVENTION

This invention provides compounds which bind to VLA-4. Such compounds can be used, for example, to assay for the presence of VLA-4 in a sample and, in pharmaceutical compositions, to inhibit cellular adhesion mediated by VLA-4, for example, binding of VCAM-1 to VLA-4. The compounds of this invention have a binding affinity to VLA-4 as expressed by an IC_{50} of about $15 \mu M$ or less (as measured using the procedure shown in Example 203 below) which compounds are defined by formula I below:



where

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl;

R^2 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and R^1 and R^2 together with the nitrogen atom bound to R^2 and the SO_2 group bound to R^1 can form a heterocyclic or a substituted heterocyclic group;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 can form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted, the substituent on said saturated substituted heterocyclic group is not carboxyl;

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl;

x is an integer of from 1 to 4;

Q is $-C(X)NR^7$ wherein R^7 is selected from the group consisting of hydrogen and alkyl;

5 X is selected from the group consisting of oxygen and sulfur;

R^5 is $-CH_2X$ where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, 10 carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

15 with the further provisos that:

A. R^5 is not selected from the group consisting of $-(CH_2)_n$ -aryl and $-(CH_2)_n$ -heteroaryl where n is an integer equal to 1 to 4 when R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a saturated heterocyclic group or a saturated substituted heterocyclic 20 group;

B. R^5 is not $-(CH_2)_x$ -Ar- $R^{5'}$ where $R^{5'}$ is selected from the group consisting of $-O-Z-NR^8R^{8'}$ and $-O-Z-R^{12}$ wherein Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl, x is an integer of from 1 to 4, R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, 25 alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, and substituted heterocyclic; and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycles and substituted heterocycles, and Z is selected from the group consisting of $-C(O)-$ and $-SO_2-$;

- C. R^5 is not $-(CH_2)_x-Ar-R^{5'}$ where Ar is aryl, substituted aryl, heteroaryl or substituted heteroaryl, x is an integer of from 1 to 4, $R^{5'}$ is selected from the group consisting of $-NR^{24}C(Z')NR^8R^{8'}$ and $-NR^{24}C(Z')R^{13}$ wherein Z' is selected from the group consisting of oxygen, sulfur and NR^{24} , R^{24} is selected from the group consisting of hydrogen, alkyl and aryl, R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl provided that when Z' is oxygen, at least one of R^8 and $R^{8'}$ is substituted alkyl, cycloalkyl, substituted cycloalkyl, saturated heterocyclic other than morpholino and thiomorpholino, substituted heterocyclic or R^8 and $R^{8'}$ are joined to form a saturated heterocycle other than morpholino or thiomorpholino, a saturated substituted heterocycle or a saturated/unsaturated heterocycle having an amino group substituted with an alkoxy carbonyl substituent, and further provided that when Z' is sulfur, at least one of R^8 and $R^{8'}$ is a group other than aryl, substituted aryl, heteroaryl or substituted heteroaryl, and R^{13} is selected from the group consisting of substituted heterocycles and saturated heterocycles other than morpholino and thiomorpholino;
- D. R^5 is not $-ALK-X$ where ALK is an alkyl group of from 1 to 10 carbon atoms attached via a methylene group $(-CH_2-)$ to the carbon atom to which it is attached; X is selected from the group consisting of substituted alkylcarbonylamino, substituted alkenylcarbonylamino, substituted alkynylcarbonylamino, heterocyclcarbonylamino, substituted heterocyclcarbonylamino, acyl, acyloxy, aminocarbonyloxy, acylamino, oxycarbonylamino, alkoxy carbonyl, substituted alkoxy carbonyl, aryloxy carbonyl, substituted aryloxy carbonyl, cycloalkoxy carbonyl, substituted cycloalkoxy carbonyl, heteroaryloxy carbonyl, substituted heteroaryloxy carbonyl, heterocyclloxy carbonyl, substituted heterocyclloxy carbonyl, cycloalkyl, substituted cycloalkyl, saturated heterocyclic, substituted saturated heterocyclic, substituted alkoxy,

substituted alkenoxy, substituted alkynoxy, heterocycloxy, substituted heterocycloxy, substituted thioalkyl, substituted thioalkenyl, substituted thioalkynyl, aminocarbonylamino, aminothiocarbonylamino, guanidino, amidino, alkylamidino, thioamidino, halogen, cyano, nitro, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-cycloalkyl, -OS(O)₂-substituted cycloalkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-cycloalkyl, -NRS(O)₂-substituted cycloalkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-cycloalkyl, -NRS(O)₂-NR-substituted cycloalkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is hydrogen or alkyl, -S(O)₂-alkyl, -S(O)₂-substituted alkyl, -S(O)₂-aryl, -S(O)₂-substituted aryl, -S(O)₂-substituted heteroaryl, -S(O)₂-substituted heteroaryl, -S(O)₂-heterocyclic, -S(O)₂-substituted heterocyclic, mono- and di-(substituted alkyl)amino, N,N-(alkyl, substituted alkyl)amino, N,N-(aryl, substituted alkyl)amino, N,N-(substituted aryl, substituted alkyl)amino, N,N-(heteroaryl, substituted alkyl)amino, N,N-(substituted heteroaryl, substituted alkyl)amino, N,N-(heterocyclic, substituted alkyl)amino, N,N-N,N-(substituted heterocyclic, substituted alkyl)amino, mono- and di-(heterocyclic)amino, mono- and di-(substituted heterocyclic)amino, N,N-(alkyl, heterocyclic)amino, N,N-(alkyl, substituted heterocyclic)amino, N,N-(aryl, heterocyclic)amino, N,N-(substituted aryl, heterocyclic)amino, N,N-(aryl, substituted heterocyclic)amino, N,N-(substituted aryl, substituted heterocyclic)amino, N,N-(heteroaryl, heterocyclic)amino, N,N-(heteroaryl, substituted heterocyclic)amino, N,N-(substituted heteroaryl, heterocyclic)amino, and N,N-(substituted heteroaryl, substituted heterocyclic)amino; and

E. R^5 is not $-(CH_2)_x-Ar-R^{5'}$ where $R^{5'}$ is a substituent selected from the group consisting of:

- (a) substituted alkylcarbonylamino with the proviso that at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino,
- 5 thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-
- 10 cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl,
- 15 substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$ -alkyl, $-OS(O)_2$ -
- 20 substituted alkyl, $-OS(O)_2$ -aryl, $-OS(O)_2$ -substituted aryl, $-OS(O)_2$ -heteroaryl, $-OS(O)_2$ -substituted heteroaryl, $-OS(O)_2$ -heterocyclic, $-OS(O)_2$ -substituted heterocyclic, $-OSO_2$ -NRR, $-NRS(O)_2$ -alkyl, $-NRS(O)_2$ -substituted alkyl, $-NRS(O)_2$ -aryl, $-NRS(O)_2$ -substituted aryl, $-NRS(O)_2$ -heteroaryl, $-NRS(O)_2$ -substituted heteroaryl, $-NRS(O)_2$ -heterocyclic,
- 25 $-NRS(O)_2$ -substituted heterocyclic, $-NRS(O)_2$ -NR-alkyl, $-NRS(O)_2$ -NR-substituted alkyl, $-NRS(O)_2$ -NR-aryl, $-NRS(O)_2$ -NR-substituted aryl, $-NRS(O)_2$ -NR-heteroaryl, $-NRS(O)_2$ -NR-substituted heteroaryl, $-NRS(O)_2$ -NR-heterocyclic, $-NRS(O)_2$ -NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino,
- 30 mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino,

mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, substituted alkyl groups
5 having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like), and alkyl/substituted alkyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-
10 substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl;

(b) alkoxyaryl substituted on the alkoxy moiety with a substituent selected from the group consisting of carboxyl and -COOR²³ where R²³ is alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl or heterocyclic,

(c) aryl and heteroaryl;

15 (d) -NR'R' wherein each R' is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclic and substituted heterocyclic with the proviso that at least one of R' is substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic and substituted
20 heterocyclic and with the further proviso that when R' is substituted alkyl at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino,
25 aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl,
30 substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl,

substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines having different substituents, wherein the substituents are selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like), and alkyl/substituted alkyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl;

(e) -alkoxy-NR"R" wherein each R" is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl,

heterocyclic, and substituted heterocyclic with the proviso that when each R¹ is substituted alkyl then at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiobonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl,

substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like), and alkyl/substituted alkyl groups substituted with -

5 SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl;

(f) substituted alkenyl or substituted alkynyl with the proviso that at

10 least one of the substituents on the substituted alkenyl/alkynyl moiety is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic with the proviso that when substituted with substituted alkyl, then at least one of the substituents

15 on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl,

20 carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl,

25 thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -

30 OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-

substituted heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted
 alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -
 NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-
 substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted
 5 alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-
 heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic,
 -NRS(O)₂-NR-substituted heterocyclic or mono- and di-alkylamino, mono-
 and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-
 (substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-
 10 (substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and
 di-(substituted heterocyclic) amino, unsymmetric di-substituted amines
 having different substituents selected from the group consisting of alkyl,
 substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,
 heterocyclic and substituted heterocyclic, substituted alkyl groups having
 15 amino groups blocked by conventional blocking groups (such as Boc, Cbz,
 formyl, and the like) and alkyl/substituted alkyl groups substituted with -
 SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -
 SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl,
 -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-
 20 substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl;

(g) substituted aryloxy and substituted heteroaryloxy with the proviso
 that at least one substituent on the substituted aryloxy/heteroaryloxy is other
 than halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy,
 alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy,
 25 alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino,
 alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino,
 alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(h) -alkoxy-saturated heterocyclic, -alkoxy-saturated substituted
 heterocyclic, -substituted alkoxy-heterocyclic and -substituted alkoxy-
 30 substituted saturated heterocyclic;

(i) -O-heterocyclic and -O-substituted heterocyclic;

(j) tetrazolyl;

(k) -NR-SO₂-substituted alkyl where R is hydrogen, alkyl or aryl, with the proviso that at least one substituent on the alkyl moiety of the substituted alkylsulfonylamino is other than halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(l) alkenylsulfonylamino, alkynylsulfonylamino, substituted alkenylsulfonylamino and substituted alkynylsulfonylamino;

(m) substituted alkoxy with the proviso that the substitution on the alkyl moiety of said substituted alkoxy does not include alkoxy-NR "R" as defined above, unsaturated heterocyclyl, alkyloxy, aryloxy, heteroaryloxy, aryl, heteroaryl or aryl/heteroaryl substituted with halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(n) amidine and amidine substituted with from 1 to 3 substituents independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic;

(o) -C(O)NR^{'''}R^{'''} where each R^{'''} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when one R^{'''} is unsaturated heterocyclic, aryl, heteroaryl or aryl/heteroaryl substituted with halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl,

alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea, then the other R''' is alkyl, substituted alkyl (other than
 5 unsaturated heterocyclyl substituted-alkyl), cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heterocyclic or substituted heterocyclic;

(p) -NR²²C(O)-R¹⁸ where R¹⁸ is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted
 10 aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, and R²² is alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

(q) -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted
 15 heteroaryl or -SO₂-alkyl;

(r) -NR'C(O)NR¹⁹R¹⁹ wherein R' is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and each R¹⁹ is independently selected from the
 20 group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

(s) -NR'C(O)OR¹⁹ wherein R' is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and R¹⁹ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;
 25

(t) -aminocarbonyl-(N-formylheterocyclyl); and

(u) -alkyl-C(O)NH-heterocyclyl and -alkyl-C(O)NH-substituted
 30 heterocyclyl;

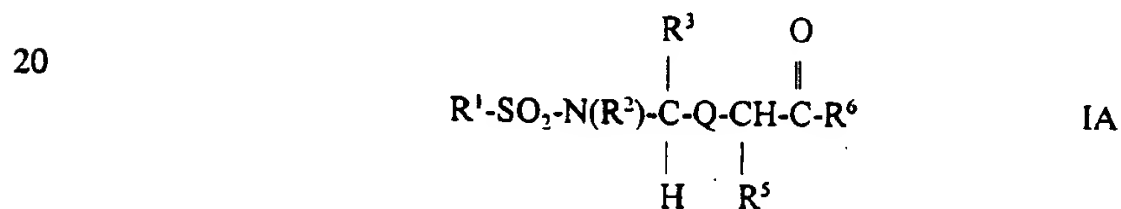
and pharmaceutically acceptable salts thereof;
and still further with the following provisos excluding the following
compounds:

5 A. when R¹ is *p*-methylphenyl, R² and R³ together with their pendent
nitrogen and carbon atoms form a pyrrolidinyl ring and Q is -C(O)NH-, then
R⁵ is not -CH₂COOH or -CH₂CH₂COOH; and

B. when R¹ is *p*-methylphenyl, R² and R³ together with their pendent
nitrogen and carbon atoms form a pyrrolidinyl ring and Q is -C(O)NH-, then
R⁵ is not 2,4,6-trimethylbenzyl.

10

In another embodiment, the compounds of this invention can also be
provided as prodrugs which convert (e.g., hydrolyze, metabolize, etc.) *in vivo*
to a compound of formula I above. In a preferred example of such an
embodiment, the carboxylic acid in the compound of formula I is modified
15 into a group which, *in vivo*, will convert to the carboxylic acid (including
salts thereof). In a particularly preferred embodiment, such prodrugs are
represented by compounds of formula IA:



25 where

R¹ is selected from the group consisting of alkyl, substituted alkyl,
aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic,
substituted heterocyclic, heteroaryl and substituted heteroaryl;

30 R² is selected from the group consisting of hydrogen, alkyl,
substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted
cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl,
heteroaryl, and substituted heteroaryl, and R¹ and R² together with the

nitrogen atom bound to R^2 and the SO_2 group bound to R^1 can form a heterocyclic or a substituted heterocyclic group;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic, and R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 can form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted, the substituent on said saturated substituted heterocyclic group is not carboxyl;

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl;

x is an integer of from 1 to 4;

R^6 is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3- β -yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl, -NH(CH₂)_pCOOY where p is an integer of from 1 to 8 and Y is as defined above, -OCH₂NR⁹R¹⁰ where R⁹ is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and R¹⁰ is selected from the group consisting of hydrogen and -CH₂COOR¹¹ where R¹¹ is alkyl, and -NHSO₂Z" where Z" is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

Q is -C(X)NR⁷- wherein R⁷ is selected from the group consisting of hydrogen and alkyl;

X is selected from the group consisting of oxygen and sulfur;

R⁵ is -CH₂X where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic,

carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

5 with the further provisos that:

A. R^5 is not selected from the group consisting of $-(CH_2)_n$ -aryl and $-(CH_2)_n$ -heteroaryl where n is an integer equal to 1 to 4 when R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a saturated heterocyclic group or a saturated substituted heterocyclic group;

10

B. R^5 is not $-(CH_2)_x$ -Ar- $R^{5'}$ where $R^{5'}$ is selected from the group consisting of $-O-Z-NR^8R^{8'}$ and $-O-Z-R^{12}$ wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, and substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle; R^{12} is selected from the group consisting of heterocycles and substituted heterocycles, and Z is selected from the group consisting of $-C(O)-$ and $-SO_2-$,

15

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,
 20 x is an integer of from 1 to 4;

C. R^5 is not $-(CH_2)_x$ -Ar- $R^{5'}$ where $R^{5'}$ is selected from the group consisting of $-NR^{24}C(Z')NR^8R^{8'}$ and $-NR^{24}C(Z')R^{13}$ wherein Z' is selected from the group consisting of oxygen, sulfur and NR^{24} , R^{24} is selected from the group consisting of hydrogen, alkyl and aryl, R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl provided that when Z' is oxygen, at least one of R^8 and $R^{8'}$ is substituted alkyl, cycloalkyl, substituted cycloalkyl, saturated heterocyclic other than morpholino and thiomorpholino, and substituted heterocyclic, or R^8 and $R^{8'}$ can be joined to form a saturated heterocycle other than morpholino or

25

30

thiomorpholino, a saturated substituted heterocycle or a saturated/unsaturated heterocycle having an amino group substituted with an alkoxycarbonyl substituent, and further provided that when Z' is sulfur, at least one of R⁸ and R^{8'} is a group other than aryl, substituted aryl, heteroaryl or substituted heteroaryl, R¹³ is selected from the group consisting of substituted heterocycles and saturated heterocycles other than morpholino and thiomorpholino,

Ar is aryl, substituted aryl, heteroaryl or substituted heteroaryl,
x is an integer of from 1 to 4;

10 D. R⁵ is not -ALK-X where ALK is an alkyl group of from 1 to 10 carbon atoms attached via a methylene group (-CH₂-) to the carbon atom to which it is attached; X is selected from the group consisting of substituted alkylcarbonylamino, substituted alkenylcarbonylamino, substituted alkynylcarbonylamino, heterocyclcarbonylamino, substituted heterocyclcarbonylamino, acyl, acyloxy, aminocarbonyloxy, acylamino, 15 oxycarbonylamino, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxy carbonyl, substituted aryloxy carbonyl, cycloalkoxycarbonyl, substituted cycloalkoxycarbonyl, heteroaryloxy carbonyl, substituted heteroaryloxy carbonyl, heterocyclcyloxy carbonyl, substituted heterocyclcyloxy carbonyl, cycloalkyl, substituted cycloalkyl, saturated heterocyclic, substituted saturated heterocyclic, substituted alkoxy, substituted alkenoxy, substituted alkynoxy, heterocyclcyloxy, substituted heterocyclcyloxy, substituted thioalkyl, substituted thioalkenyl, substituted thioalkynyl, aminocarbonylamino, aminothi carbonylamino, guanidino, 25 amidino, alkylamidino, thioamidino, halogen, cyano, nitro, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-cycloalkyl, -OS(O)₂-substituted cycloalkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, 30 -NRS(O)₂-cycloalkyl, -NRS(O)₂-substituted cycloalkyl, -NRS(O)₂-aryl,

-NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted
 heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic,
 -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-
 cycloalkyl, -NRS(O)₂-NR-substituted cycloalkyl, -NRS(O)₂-NR-aryl,
 5 -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-
 substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted
 heterocyclic where R is hydrogen or alkyl, -S(O)₂-alkyl, -S(O)₂-substituted
 alkyl, -S(O)₂-aryl, -S(O)₂-substituted aryl, -S(O)₂-substituted heteroaryl,
 -S(O)₂-substituted heteroaryl, -S(O)₂-heterocyclic, -S(O)₂-substituted
 10 heterocyclic, mono- and di-(substituted alkyl)amino, N,N-(alkyl, substituted
 alkyl)amino, N,N-(aryl, substituted alkyl)amino, N,N-(substituted aryl,
 substituted alkyl)amino, N,N-(heteroaryl, substituted alkyl)amino, N,N-
 (substituted heteroaryl, substituted alkyl)amino, N,N-(heterocyclic,
 substituted alkyl)amino, N,N-N,N-(substituted heterocyclic, substituted
 15 alkyl)amino, mono- and di-(heterocyclic)amino, mono- and di-(substituted
 heterocyclic)amino, N,N-(alkyl, heterocyclic)amino, N,N-(alkyl, substituted
 heterocyclic)amino, N,N-(aryl, heterocyclic)amino, N,N-(substituted aryl,
 heterocyclic)amino, N,N-(aryl, substituted heterocyclic)amino, N,N-
 (substituted aryl, substituted heterocyclic)amino, N,N-(heteroaryl,
 20 heterocyclic)amino, N,N-(heteroaryl, substituted heterocyclic)amino, N,N-
 (substituted heteroaryl, heterocyclic)amino, and N,N-(substituted heteroaryl,
 substituted heterocyclic)amino; and

E. R³ is not -(CH₂)_x-Ar-R^{3'} where R^{3'} is a substituent selected
 from the group consisting of:

25 (a) substituted alkylcarbonylamino with the proviso that at least one
 of the substituents on the substituted alkyl moiety is selected from the group
 consisting of alkoxy, substituted alkoxy, acyl, acylamino,
 thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino,
 thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino,
 30 aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen,
 hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-

cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-
 substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl,
 carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl,
 substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl,
 5 substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl,
 substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl,
 thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted
 heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy,
 substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy,
 10 oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-
 substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl,
 -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted
 heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl,
 -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-
 15 substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted
 heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -
 NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl,
 -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-
 NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-
 20 (substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted
 aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted
 heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-
 (substituted heterocyclic) amino, unsymmetric di-substituted amines having
 different substituents selected from the group consisting of alkyl, substituted
 25 alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic
 and substituted heterocyclic, substituted alkyl groups having amino groups
 blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the
 like) and alkyl/substituted alkyl groups substituted with -SO₂-alkyl, -SO₂-
 substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl,
 30 -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-

heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl;

(b) alkoxyaryl substituted on the alkoxy moiety with a substituent selected from the group consisting of carboxyl and -COOR²³ where R²³ is
5 alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl or heterocyclic;

(c) aryl and heteroaryl;

(d) -NR'R' wherein each R' is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclic and
10 substituted heterocyclic with the proviso that at least one of R' is substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic or substituted heterocyclic and with the further proviso that when R' is substituted alkyl at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino,
15 thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl,
20 carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl,
25 thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl,
30 -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl,

-NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-
 substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted
 heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl,
 -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-
 5 heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic,
 -NRS(O)₂-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and
 di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-
 (substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-
 (substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and
 10 di-(substituted heterocyclic) amino, unsymmetric di-substituted amines
 having different substituents selected from the group consisting of alkyl,
 substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,
 heterocyclic and substituted heterocyclic, substituted alkyl groups having
 amino groups blocked by conventional blocking groups (such as Boc, Cbz,
 15 formyl, and the like) and alkyl/substituted alkyl groups substituted with -
 SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -
 SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -
 SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-
 substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl;
 20 (e) -alkoxy-NR''R'' wherein each R'' is independently selected from
 the group consisting of alkyl, substituted alkyl, aryl, substituted aryl,
 cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl,
 heterocyclic, and substituted heterocyclic with the proviso that when each R''
 is substituted alkyl then at least one of the substituents on the substituted
 25 alkyl moiety is selected from the group consisting of alkoxy, substituted
 alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino,
 amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino,
 aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy,
 cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-
 30 substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl,
 carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-

substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted
 heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone,
 thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl,
 thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted
 5 thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic,
 substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy,
 heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted
 heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl,
 OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-
 10 heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-
 substituted heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted
 alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl,
 NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-
 substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted
 15 alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-
 heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic,
 -NRS(O)₂-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and
 di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-
 (substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-
 20 (substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and
 di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines
 having different substituents selected from the group consisting of alkyl,
 substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,
 heterocyclic and substituted heterocyclic, substituted alkyl groups having
 25 amino groups blocked by conventional blocking groups (such as Boc, Cbz,
 formyl, and the like) and alkyl/substituted alkyl groups substituted with -
 SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -
 SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl,
 -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-
 30 substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl;

(f) substituted alkenyl or substituted alkynyl with the proviso that at least one of the substituents on the substituted alkenyl/alkynyl moiety is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic with the proviso that when substituted with substituted alkyl then at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-

(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and alkyl/substituted alkyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl;

(g) substituted aryloxy and substituted heteroaryloxy with the proviso that at least one substituent on the substituted aryloxy/heteroaryloxy is other than halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(h) -alkoxy-saturated heterocyclic, -alkoxy-saturated substituted heterocyclic, -substituted alkoxy-heterocyclic and -substituted alkoxy-substituted saturated heterocyclic;

(i) -O-heterocyclic and -O-substituted heterocyclic;

(j) tetrazolyl;

(k) -NR-SO₂-substituted alkyl where R is hydrogen, alkyl or aryl, with the proviso that at least one substituent on the alkyl moiety of the substituted alkylsulfonylamino is other than halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl,

alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(l) alkenylsulfonylamino, alkynylsulfonylamino, substituted alkenylsulfonylamino and substituted alkynylsulfonylamino;

5 (m) substituted alkoxy with the proviso that the substitution on the alkyl moiety of said substituted alkoxy does not include alkoxy-NR''R'' as defined above, unsaturated heterocyclic, alkyloxy, aryloxy, heteroaryloxy, aryl, heteroaryl or aryl/heteroaryl substituted with halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-
10 dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(n) amidine and amidine substituted with from 1 to 3 substituents
15 independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic;

(o) -C(O)NR'''R''' where each R''' is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted
20 cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when one R''' is unsaturated heterocyclic, aryl, heteroaryl or aryl/heteroaryl substituted with halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl,
25 alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea, then the other R''' is alkyl, substituted alkyl (other than unsaturated heterocyclyl substituted-alkyl), cycloalkyl, substituted
30 cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heterocyclic or substituted heterocyclic;

(p) $-NR^{22}C(O)-R^{18}$ where R^{18} is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, and R^{22} is alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

(q) $-SO_2$ -aryl, $-SO_2$ -substituted aryl, $-SO_2$ -heteroaryl, $-SO_2$ -substituted heteroaryl or $-SO_2$ -alkyl;

(r) $-NR'C(O)NR^{19}R^{19}$ wherein R' is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and each R^{19} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

(s) $-NR'C(O)OR^{19}$ wherein R' is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and R^{19} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

(t) -aminocarbonyl-(N-formylheterocyclyl); and

(u) -alkyl-C(O)NH-heterocyclyl and -alkyl-C(O)NH-substituted heterocyclyl;

and pharmaceutically acceptable salts thereof;

with the following additional proviso:

when R^1 is *p*-methylphenyl, R^2 and R^3 together with their pendent nitrogen and carbon atoms form a pyrrolidinyl ring, R^5 is *p*-[-OCH₂CH₂-(4,5-dihydroimidazol-2-yl)], Q is -C(O)NH-, then R^6 is not -O-methyl.

Preferred compounds within the scope of formulas I and IA above include by way of example the following:

N-(Toluene-4-sulfonyl)-L-prolyl-4-(α -methylbenzyloxy)-L-phenylalanine

5 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-tyrosine

N-(Toluene-4-sulfonyl)-L-prolyl-4-carboxyphenylalanine

10 *N*-(Toluene-4-sulfonyl)-L-prolyl-3-(carboxy)phenylalanine

N-(Toluene-4-sulfonyl)-L-prolyl-4-(2-carboxyphenoxy)-L-phenylalanine

N-(Toluene-4-sulfonyl)-L-prolyl-O-(benzyl)-L-tyrosine

15 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-(iodo)-L-phenylalanine

N-(Toluene-4-sulfonyl)-L-prolyl-L-4-(methoxy)-phenylalanine

20 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-nitro-L-phenylalanine

N-(Toluene-4-sulfonyl)-L-prolyl-4-(*O*-*tert*-butyl)-L-tyrosine

N-(Toluene-4-sulfonyl)-L-prolyl-L-(3,5-diiodo)-tyrosine

25 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(aminobenzoyl)-phenylalanine

N-(Toluene-4-sulfonyl)-L-prolyl-L-(3-iodo-4-hydroxy)-phenylalanine

30 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-chloro)phenylalanine

N-(Toluene-4-sulfonyl)-L-prolyl-L-leucine

N-(Toluene-4-sulfonyl)-L-prolyl-L-alanine

35 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(acetamido)-phenylalanine

N-(Toluene-4-sulfonyl)-L-prolyl-L-isoleucine

40 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-aspartic acid

N-(Toluene-4-sulfonyl)-L-prolyl-L-lysine

N-(Toluene-4-sulfonyl)-L-prolyl-L-glutamic acid

- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-dibenzylamino)-phenylalanine methyl ester
- 5 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(*N*-benzyl)-histidine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-dibenzylamino)-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-methionine
- 10 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-serine
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-(*N*-benzyl)-histidine
- 15 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(1-methyl)histidine
- N*-(Toluene-4-sulfonyl)-L-prolyl-D-(*N*-benzyl)histidine
- N*-(Toluene-4-sulfonyl)-L-glutamyl-L-tyrosine
- 20 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(*N*-3-methyl)histidine
- N*-(Toluene-4-sulfonyl)-L-prolyl- α -amino-2,3-dihydro-(1,4-benzodioxin)-6-propanoic acid
- 25 *N*-(Toluene-4-sulfonyl)-L-prolyl- α -amino-1,3-benzodioxole-5-propanoic acid
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-valine
- 30 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-iodo)-phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(aminobenzoyl)phenylalanine methyl ester
- 35 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-chloro)phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-amino)phenylalanine methyl ester
- 40 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-acetamido)phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-(*N*-benzyl)-histidine methyl ester
- 45 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-(3-3'-tolylureido)-L-phenylalanine

- N*-(Toluene-4-sulfonyl)-L-prolyl-4-[(2,3,3a,7a-tetrahydro-1H-indole-2-carbonyl)-amino]-L-phenylalanine
- 5 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-pentylamino)phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-*O*-(2-dibenzylamino-ethyl)-tyrosine methyl ester
- 10 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-*O*-[2-(dibenzylamino)ethyl]-tyrosine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-pentylamino)phenylalanine
- 15 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(4-chlorobenzylamino)-phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[3-(4-cyanophenyl)-ureido]-phenylalanine methyl ester
- 20 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[3-(4-cyanophenyl)-ureido]-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-*O*-(*tert*-butoxycarbonylmethyl)-tyrosine methyl ester
- 25 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-*O*-(*tert*-butoxycarbonylmethyl)-tyrosine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[(3*S*)-3,4-dihydro-isoquinolin-3-yl-aminocarbonyl]-phenylalanine
- 30 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-[3-(3-methoxy-phenyl)-ureido]-L-phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-[3-(3-methoxy-phenyl)-ureido]-L-phenylalanine
- 35 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-*O*-(4,5-dihydro-1H-imidazol-2-yl-methyl)-tyrosine
- 40 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(3-propyl-ureido)-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-benzylamino)phenylalanine
- 45 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-benzylamino)phenylalanine methyl ester

- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(4-chlorobenzylamino)-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-chloromethanesulfonylamino)-phenylalanine
- 5 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-(aminobenzoyl)phenylalanine methyl ester
- 10 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-(benzamido)phenylalanine
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-tyrosine ethyl ester
- 15 *N*-(Toluene-4-Sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-tyrosine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[(pyridin-4-yl)methylamino]phenylalanine
- 20 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[(pyridin-4-yl)methylamino]phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-(pyridin-3-carboxamido)phenylalanine methyl ester
- 25 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-(pyridine-3-carboxamido)phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[(pyridin-3-yl)methylamino]phenylalanine
- 30 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-nitrophenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-nitrophenylalanine ethyl ester
- 35 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-methoxybenzamido)phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-(4-nitro)phenylalanine ethyl ester
- 40 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-bromobenzamido)phenylalanine ethyl ester
- 45 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiamorphyl-L-4-aminophenylalanine ethyl ester

- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-acetamidophenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-methoxybenzamido)phenylalanine
- 5 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-acetamidophenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-acetamidophenylalanine
- 10 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-acetamidophenylalanine isopropyl ester
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-L-4-(isonicotinamido)phenylalanine ethyl ester
- 15 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(isonicotinamido)phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(π -toluene-4-sulfonyl)histidine methyl ester
- 20 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-(nicotinamido)phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(*O*-methyl)tyrosine ethyl ester
- 25 *N*-(α -Toluenesulfonyl)-L-prolyl-L-4-(isonicotinamido)phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-bromobenzamido)phenylalanine
- 30 *N*-(α -Toluenesulfonyl)-L-prolyl-L-4-(isonicotinamido)phenylalanine
- N*-(Toluene-4-sulfonyl)-L-(1,1-dioxo)thiamorpholyl-L-4-(2-bromobenzamido))phenylalanine ethyl ester
- 35 *N*-(Toluene-4-sulfonyl)-L-(1,1-dioxo)thiamorpholyl-L-4-(2-bromobenzamido)phenylalanine
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-L-4-(isonicotinamido)phenylalanine
- 40 *N*-(α -Toluenesulfonyl)-L-prolyl-L-4-(2-bromobenzamido)phenylalanine ethyl ester
- 45

- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-tyrosine isopropyl ester
- 5 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-tyrosine *tert*-butyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-tyrosine *tert*-butyl ester
- 10 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-trifluoromethylbenzamido)phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-methylbenzamido)phenylalanine ethyl ester
- 15 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-trifluoromethylbenzamido)phenylalanine
- N*-(4-Fluorobenzenesulfonyl)-L-thiaprolyl-L-tyrosine *tert*-butyl Ester
- 20 *N*-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-tyrosine *tert*-butyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-(dimethylamino)-L-phenylalanine
- 25 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-[(2-bromo)benzamido]-L-phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-[(pyrazin-2-yl)C(O)NH]-L-phenylalanine methyl ester
- 30 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-(4-nitrobenzoyl)-L-phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-4-(2-bromobenzamido)-L-phenylalanine *t*-butyl ester
- 35 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-4-(2-bromobenzamido)-L-phenylalanine *t*-butyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-(1-H-2-oxo-3-methyltetrahydropyrimidin-1-yl)-L-phenylalanine *t*-butyl ester
- 40 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-(1-H-2-oxo-3-methyltetrahydropyrimidin-1-yl)-L-phenylalanine
- 45

- N-(Toluene-4-sulfonyl)-L-prolyl-3-chloro-4-(t-butoxy)-L-phenylalanine t-butyl ester
- 5 N-(Toluene-4-sulfonyl)-L-prolyl-3-chloro-4-(hydroxy)-L-phenylalanine t-butyl ester
- N-(Toluene-4-sulfonyl)-L-prolyl-4-(N,N-dimethylureido)-L-phenylalanine t-butyl ester
- 10 N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-chloro-4-(hydroxy)-L-phenylalanine t-butyl ester
- N-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-chloro-4-(hydroxy)-L-phenylalanine isopropyl ester
- 15 N-(Toluene-4-sulfonyl)-L-prolyl-4-(2-methoxyphenyl)-L-phenylalanine t-butyl ester
- N-(Toluene-4-sulfonyl)-L-prolyl-4-(2-methoxyphenyl)-L-phenylalanine
- 20 N-(Toluene-4-sulfonyl)-L-prolyl-[(5-N,N-dimethyl ureido)-pyridin-2-yl]-alanine
- N-(Toluene-4-sulfonyl)-L-prolyl-4-(N,N-dimethylsulfamyl)-L-phenylalanine
- 25 N-(Toluene-4-sulfonyl)-L-prolyl-4-(N¹,N¹,N²-trimethylsulfamyl)-L-phenylalanine
- N-(Toluene-4-sulfonyl)-L-prolyl-(1-t-butoxycarbonylmethylimidazol-4-yl)-L-alanine methyl ester
- 30 N-(Toluene-4-sulfonyl)-L-prolyl-[N,N-dimethylaminocarbonylmethylimidazol-4-yl]-L-alanine methyl ester
- 35 N-[4-(dimethyl ureylenyl)-benzenesulfonyl]-L-prolyl-4-hydroxy-L-phenylalanine isopropyl ester
- N-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-chloro-4-hydroxy-L-phenylalanine isopropyl ester
- 40 N-(Toluene-4-sulfonyl)-L-prolyl-3-chloro-4-hydroxy-L-phenylalanine isopropyl ester
- N-(Toluene-4-sulfonyl)-L-prolyl-4-(carboxymethyl)-L-phenylalanine methyl ester
- 45

- N-(Toluene-4-sulfonyl)-L-prolyl-4-(2-methylbenzamido)-L-phenylalanine methyl ester
- 5 N-(Toluene-4-sulfonyl)-L-prolyl-4-(N,N-dimethylaminocarbonylmethyl)-L-phenylalanine
- N-(1-methylimidazol-4-sulfonyl)-L-prolyl-4-hydroxy-L-phenylalanine isopropyl ester
- 10 N-(Toluene-4-sulfonyl)-L-prolyl-4-(2,4,5-trioxo-3-phenyltetrahydroimidazol-1-yl)-L-phenylalanine isopropyl ester
- N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-fluoro-4-hydroxy-L-phenylalanine isopropyl ester
- 15 N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-chloro-4-t-butoxy-L-phenylalanine t-butyl ester
- N-{N-[(1S)-2,10-camphorsultamyl]acetyl}-L-tyrosine t-butyl ester
- 20 N-{N-[(1S)-2,10-camphorsultamyl]acetyl}-3-chlorotyrosine isopropyl ester
- N-(4-Fluorobenzenesulfonyl)-L-thiaprolyl-4-hydroxy-L-phenylalanine t-butyl ester
- 25 N-(Toluene-4-sulfonyl)-L-prolyl-4-(N,N-dimethylaminocarbonylmethyl)-L-phenylalanine t-butyl ester
- N-(4-Nitrobenzenesulfonyl)-L-prolyl-4-(hydroxy)-L-phenylalanine t-butyl ester
- 30 N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-4-hydroxy-L-phenylalanine isopropyl ester
- 35 N-(4-Fluorobenzenesulfonyl)-L-prolyl-4-hydroxy-L-phenylalanine t-butyl ester
- N-(pyridin-3-sulfonyl)-L-prolyl-4-hydroxy-L-phenylalanine t-butyl ester
- 40 N-(Toluene-4-sulfonyl)-L-prolyl-4-(methanesulfonamido)-L-phenylalanine
- N-(Toluene-4-sulfonyl)-L-prolyl-4-(2,4,5-trioxo-3-(3-chlorophenyl)-tetrahydroimidazol-1-yl)-L-phenylalanine benzyl ester
- 45 N-(1-methylimidazol-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-chloro-4-hydroxy-L-phenylalanine ethyl ester.

N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl) thiapropyl-L-3-chloro-4-~~tert~~-butoxy-phenylalanine ~~tert~~-Butyl Ester

5 N-[2-(N-2,10-camphorsultamyl) acetyl]-L-3-chloro-4-hydroxyphenylalanine Isopropyl Ester

Preferably, in the compounds of formula I and IA above, R¹ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl. Even more preferably, R¹ is selected from the group consisting of 4-methylphenyl, methyl, benzyl, *n*-butyl, 4-chlorophenyl, 1-naphthyl, 2-naphthyl, 4-methoxyphenyl, phenyl, 2,4,6-trimethylphenyl, 2-(methoxycarbonyl)phenyl, 2-carboxyphenyl, 3,5-dichlorophenyl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl, 3,4-dimethoxyphenyl, 15 4-(CH₃C(O)NH-)phenyl, 4-trifluoromethoxyphenyl, 4-cyanophenyl, isopropyl, 3,5-di-(trifluoromethyl)phenyl, 4-*t*-butylphenyl, 4-*t*-butoxyphenyl, 4-nitrophenyl, 2-thienyl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl, phenethyl, 1-N-methylimidazol-4-yl, 4-bromophenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-[CH₃SC(=NH)]phenyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methyl-4-pyrazolyl, 2-thiazolyl, 5-methyl-1,3,4-thiadiazol-2-yl, 4-[H₂NC(S)]phenyl, 4-aminophenyl, 4-fluorophenyl, 20 2-fluorophenyl, 3-fluorophenyl, 3,5-difluorophenyl, pyridin-3-yl, pyrimidin-2-yl, 4-(3'-dimethylamino-*n*-propoxy)-phenyl, and 1-methylpyrazol-4-yl.

25 Preferably, in the compounds of formula I and IA above, R² is hydrogen, methyl, phenyl, benzyl, -(CH₂)₂-2-thienyl, and -(CH₂)₂-φ.

In one embodiment, R¹ and R² together with the nitrogen atom bound to R² and the SO₂ group bound to R¹ are joined to form a heterocyclic group or substituted heterocyclic group. Preferred heterocyclic and substituted heterocyclic groups include those having from 5 to 7 ring atoms and having 2 to 3 heteroatoms in the ring selected from the group consisting of nitrogen, oxygen and sulfur, which ring is optionally fused to another ring such as a

phenyl or cyclohexyl ring to provide for a fused ring heterocycle of from 10 to 14 ring atoms and having 2 to 4 heteroatoms in the ring selected from the group consisting of nitrogen, oxygen and sulfur. Specifically preferred R¹/R² joined groups include, by way of example, benzisothiazolanyl (saccharin-2-yl).

Preferably, in the compounds of formula I and IA above, R³ includes all of the isomers arising by substitution with methyl, phenyl, benzyl, diphenylmethyl, -CH₂CH₂-COOH, -CH₂-COOH, 2-amidoethyl, *iso*-butyl, *t*-butyl, -CH₂O-benzyl and hydroxymethyl.

In another preferred embodiment, R² and R³ together with the nitrogen atom bound to R² and the carbon atom bound to R³ form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted, the substituent on said saturated substituted heterocyclic group is not carboxyl.

Q is preferably -C(O)NH- or -C(S)NH-.

R⁵ is preferably selected from the group consisting of all possible isomers arising by substitution with the following groups: *p*-[-OCH(CH₃)φ]-benzyl, 4-hydroxybenzyl, 2-carboxybenzyl, 3-carboxybenzyl, 4-carboxybenzyl, 4-(2-carboxyphenoxy)benzyl, 4-(benzyloxy)benzyl, 4-iodobenzyl, 4-methoxybenzyl, 4-nitrobenzyl, 4-(*tert*-butoxy)benzyl, 3,5-diiodo-4-hydroxybenzyl, 4-(benzamido)benzyl, benzyl, 4-hydroxy-3-iodobenzyl, 4-chlorobenzyl, isobutyl, methyl, 4-(acetamido)benzyl, *n*-butyl, carboxymethyl, 4-aminobutyl, 2-carboxyethyl, 4-(*N,N*-dibenzylamino)-benzyl, (*N*-benzylimidazol-4-yl)methyl, 2-thiomethoxyethyl, hydroxymethyl, (*N*-methylimidazol-4-yl)methyl, 4-(isopropyl-C(O)NH-) butyl, 4-(benzamido)butyl, 4-(benzyl-C(O)NH-)butyl, (*N*-methylimidazol-5-yl)methyl, 4-(pyridin-2-yl-C(O)NH-)butyl, 4-(6-methylpyridin-3-yl-

C(O)NH-) butyl, 4-(3-methylthien-2-yl-C(O)NH-)butyl, 4-(pyrrol-2-yl-
 C(O)NH-)butyl, 4-(furan-2-yl-C(O)NH-)butyl, isopropyl, 4-aminobenzyl, 4-
 (4-phenylbutoxy)benzyl, 4-(1-methylindol-3-yl-C(O)NH-)butyl, 4-(4-
 methanesulfonylphenyl-C(O)NH-)butyl, 4-(4-acetylphenyl-C(O)NH-)butyl,
 5 4-(4-fluorophenyl-C(O)NH-)butyl, 4-[2-(pyridin-2-yl)ethynyl]benzyl,
 4-[2-(3-hydroxyphenyl)ethynyl]benzyl, 4-(pyridin-4-yl-C(O)NH-)benzyl,
 4-(pyridin-3-yl-C(O)NH-)benzyl, 4-(3-methylphenyl-NHC(O)NH-)benzyl,
 4-(2,3-dihydroindol-2-yl-C(O)NH-)benzyl, 4-(*N,N*-dipentylamino)benzyl,
 4-(*N*-pentylamino)benzyl, 4-[2-(*N,N*-dibenzylamino)ethoxy]benzyl,
 10 3-hydroxybenzyl, 4-(*N-n*-butyl-*N-n*-pentylamino)benzyl, 4-(*N*-4-
 chlorophenylamino)benzyl, 4-(4-cyanophenyl-NHC(O)NH-)benzyl,
 4-(carboxymethoxy)benzyl, 4-(tert-butoxycarbonylmethoxy)benzyl,
 4-(5-fluoroindol-2-yl-C(O)NH-)benzyl, 4-(1,2,3,4-tetrahydroisoquinolin-3-
 yl-C(O)NH-)benzyl, 4-(3-methoxyphenyl-NHC(O)NH-)benzyl, 4-[2-(indol-
 15 3-yl)ethoxy]benzyl, 4-(4,5-dihydroimidazol-2-ylmethoxy)benzyl, 4-(*n*-
 propyl-NHC(O)NH-)benzyl, 4-(*N*-benzylamino)benzyl, 3-methoxybenzyl, 4-
 (pyridin-2-yl-C(O)NH-)benzyl, 4-(*N*-4-chlorobenzylamino)benzyl, 4-(2-
 chloromethylsulfonylamino)benzyl, 4-(*N,N*-dimethylamino)benzyl,
 3-aminobenzyl, 4-(benzyl)benzyl, 2-hydroxyethyl, 4-nitrobenzyl, 4-(phenyl-
 20 NHC(S)NH-)benzyl, 4-(pyridin-3-yl-NHC(S)NH-)benzyl, 4-(pyridin-4-
 ylmethylamino)benzyl, 4-[ϕ CH₂OCH₂(Boc-HN)CHC(O)NH-]benzyl,
 4-(pyridin-3-yl-C(O)NH-)butyl, 4-(pyridin-4-yl-C(O)NH-)butyl, 4-(pyridin-
 3-yl-C(O)NH-)benzyl, 4-(pyridin-4-yl-C(O)NH-)benzyl, 4-(*N*-
 toluenesulfonylpyrrolidin-2-yl-C(O)NH-)butyl, 4-(piperidin-4-yl-C(O)NH-)
 25 butyl, 4-(2-Boc-1,2,3,4-tetrahydroisoquinolin-3-yl-NHCH₂-)benzyl, 4-(2-
 Boc-1,2,3,4-tetrahydroisoquinolin-3-yl-C(O)NH-)benzyl, 4-(pyridin-3-
 ylmethylamino)benzyl, 4-[ϕ CH₂O(O)C(CbzNH)CHCH₂CH₂C(O)NH-]
 benzyl, 4-(2-methoxybenzamido)benzyl, 4-(2-bromobenzamido)benzyl,
 4-(pyrazin-2-yl-C(O)NH-)benzyl, (1-toluenesulfonylimidizol-4-yl)methyl,
 30 [1-(*N,N*-dimethylaminosulfonyl)imidizol-4-yl]methyl, 4-(trifluoromethyl)-
 benzyl, 4-(3,3-dimethylureido)benzyl, 4-(methoxycarbonylamino)benzyl, 4-

(1,3,3-trimethylureido)benzyl, 4-(methoxycarbonyl-*N*-methylamino)benzyl, 4-cyanobenzyl, 4-(2-formyl-1,2,3,4-tetrahydroisoquinolin-3-yl-C(O)NH)benzyl, phenyl, 4-(aminomethyl)benzyl, 4-(1-Boc-piperidin-4-yl-C(O)NHCH₂-)benzyl, 4-(1-Boc-piperidin-4-yl-C(O)O-)benzyl, 4-(piperidin-4-yl-C(O)NHCH₂-)benzyl, 4-[(1-methylpiperidin-4-yl)-O-]benzyl, 4-(1,2,3,4-tetrahydroquinolin-2-yl-C(O)NH-)benzyl, α -methylbenzyl, 4-(trimethylacetamido)benzyl, 4-(2-methylpropionamido)benzyl, 4-(morpholin-4-yl-C(O)NH-)benzyl, 4-(3,3-diethylureido)benzyl, 4-(2-trifluoromethylbenzamido)benzyl, 4-(2-methylbenzamido)benzyl, 4-hydroxy-3-nitrobenzyl, 3-hydroxy-4-(ϕ -OC(O)NH-)benzyl, 4-(thiomorpholino-4-yl-C(O)NH-)benzyl, 4-(1,1-dioxothiomorpholino-4-yl-C(O)NH-)benzyl, 3-nitro-4-(methoxycarbonylmethoxy)benzyl, (2-benzoxazolinon-6-yl)methyl, (2H-1,4-benzoxazin-3(4H)-one-7-yl)methyl, 4-[*N,N*-dimethylaminosulfonyl-(*N*-methyl)amino]benzyl, 4-[(2-methylpyrrolidin-1-yl)-C(O)NH-]benzyl, (pyridin-4-yl)methyl, 4-(1-methylpiperidin-4-yl-C(O)NH-)benzyl, 4-[bis(*N,N*-dimethylaminothiocarbonyl)amino]benzyl, 4-(*N,N*-dimethylaminosulfonyl)-benzyl, 4-(imidazolid-2-one-1-yl)benzyl, 3,4-(ethylenedioxy)benzyl-, 3,4-(methylenedioxy)benzyl- and 4-(3-formylimidazolid-2-one-1-yl)benzyl.

20

In the compounds of formula 1A, R⁶ is preferably 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), methoxy, ethoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, cyclopentoxy, *neo*-pentoxy, 2- α -*iso*-propyl-4- β -methylcyclohexoxy, 2- β -isopropyl-4- β -methylcyclohexoxy, -NH₂, benzyloxy, -NHCH₂COOH, -NHCH₂CH₂COOH, -NH-adamantyl, -NHCH₂CH₂COOCH₂CH₃, -NHSO₂-*p*-CH₃- ϕ , -NHOR⁸ where R⁸ is hydrogen, methyl, *iso*-propyl or benzyl, O-(*N*-succinimidyl), -O-cholest-5-en-3- β -yl, -OCH₂-OC(O)C(CH₃)₃, -O(CH₂)_zNHC(O)W where *z* is 1 or 2 and W is selected from the group consisting of pyrid-3-yl, *N*-methylpyridyl, and *N*-methyl-1,4-dihydro-pyrid-3-yl, -NR''C(O)-R' where R' is aryl, heteroaryl or heterocyclic and R'' is hydrogen or -CH₂C(O)OCH₂CH₃.

30

This invention also provides methods for binding VLA-4 in a biological sample which method comprises contacting the biological sample with a compound of formula I or IA above under conditions wherein said compound binds to VLA-4.

5

Certain of the compounds of formula I and IA above are also useful in reducing VLA-4 mediated inflammation *in vivo*.

This invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of one or more of the compounds of formula I or IA above with the exception that R³ and R⁵ are derived from L-amino acids or other similarly configured starting materials. Alternatively, racemic mixtures can be used.

10
15

The pharmaceutical compositions may be used to treat VLA-4 mediated disease conditions. Such disease conditions include, by way of example, asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetes), inflammatory bowel disease (including ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

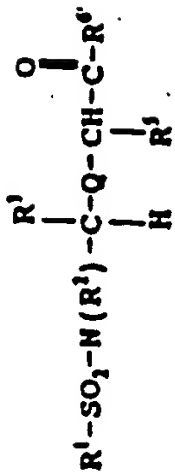
20
25

Accordingly, this invention also provides methods for the treatment of an inflammatory disease in a patient mediated by VLA-4 which methods comprise administering to the patient the pharmaceutical compositions described above.

30

Preferred compounds of formula I and IA above include those set forth in Tables IA and IB below.

Table 1A



R ¹	R ²	R ³	R ⁴	R ⁵	Q = -C(O)NR ² - R ²
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>p</i> -[OCH(CH ₃)φ]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>p</i> -hydroxybenzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>o</i> -carboxybenzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>p</i> -carboxybenzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>m</i> -carboxybenzyl-	-OH	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ -
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[O-(<i>o</i> -carboxyphenyl)]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -benzyloxybenzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -iodobenzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -methoxybenzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -nitrobenzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -(<i>t</i> -butoxy)benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			(3,5-diodo-4-hydroxyphenyl)-CH ₂ -	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[-NHC(O)φ]-benzyl-	-OH	H

R ¹	R ²	R ³	R ³	R ³	R ⁴	Q = $\begin{smallmatrix} \text{C(O)NR}^2 \\ \text{R}^3 \end{smallmatrix}$
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			(4-hydroxy-3-iodophenyl)-CH ₂ -	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -chlorobenzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			isobutyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			methyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			4-[-NHC(O)CH ₃]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>n</i> -butyl-	-OH	H
<i>p</i> -C.I.-φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			CH ₂ -COOH	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			H ₂ N-(CH ₂) ₄ -	-OH	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ -
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			-CH ₂ CH ₂ -COOH	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -(dibenzylamino)-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			1-N-benzylimidazol-4-yl-CH ₂ -	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -(dibenzylamino)-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			CH ₂ SCCH ₂ CH ₂ -	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			HOCH ₂ -	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ S-C(CH ₃) ₂ - (L-5,5-dimethylthiazolidin-4-yl)			1-N-benzylimidazol-4-yl-CH ₂ -	-OH	H

R ¹	R ²	R ³	R ⁴	Q = -C(O)NR ⁷ -
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		1-N-methylimidazol-4-yl-CH ₂ -	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		1-N-benzylimidazol-4-yl-CH ₂ -	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>i</i> -propyl-C(O)NH-(CH ₂) ₄ -	H
3,5-trifluoro- methylphenyl	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>i</i> -propyl-C(O)NH-(CH ₂) ₄ -	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>i</i> -butyl-C(O)NH-(CH ₂) ₄ -	H
3,5-trifluoro- methylphenyl	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>i</i> -butyl-C(O)NH-(CH ₂) ₄ -	H
<i>p</i> -Cl ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		phenyl-C(O)NH-(CH ₂) ₄ -	H
3,5-trifluoro- methylphenyl	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		phenyl-C(O)NH-(CH ₂) ₄ -	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = $\begin{smallmatrix} \text{C}(\text{O})\text{NR}^7 \\ \text{R}^7 \end{smallmatrix}$
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			benzyl-C(O)NH-(CH ₂) ₄ -	-OH	H
3,5-trifluoro- methylphenyl	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			benzyl-C(O)NH-(CH ₂) ₄ -	-OH	H
<i>p</i> -CH ₃ -φ-	H	-(CH ₂) ₄ COOH (L isomer)		<i>p</i> -hydroxybenzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			1-N-methylimidazol-5-yl-CH ₂ -	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			3,4-(ethylenedioxy)benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			3,4-(methylenedioxy)benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			pyrid-2-yl-C(O)NH-(CH ₂) ₄ -	-OH	H

R ¹	R ²	R ³	R ⁵	R ⁶	Q = $\begin{smallmatrix} \text{C(O)NR}^7 \\ \\ \text{R}^7 \end{smallmatrix}$
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		6-methylpyrid-3-yl-C(O)NH-(CH ₂) ₄ -	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		3-methylthien-2-yl-C(O)NH-(CH ₂) ₄ -	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		pyrrol-2-yl-C(O)NH-(CH ₂) ₄ -	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		furan-2-yl-C(O)NH-(CH ₂) ₄ -	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		-CH(CH ₃) ₂	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -iodobenzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[-NHC(O)-φ]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -chlorobenzyl-	-OCH ₃	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ - R ⁷
<i>p</i> -C ₆ H ₄ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -aminobenzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[NHC(O)CH ₃]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic -CH ₂ S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)			1-N-benzylimidazol-4-yl-CH ₂ -	-OCH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[φ(CH ₂) ₄ O]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			1-N-benzylimidazol-4-yl-CH ₂ -	-OCH ₃ CH ₂ - NHC(O)-pyrid- 3-yl	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			-(CH ₂) ₄ NHC(O)-(1-methylindol-3-yl)	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			-(CH ₂) ₄ NHC(O)-[<i>p</i> -SO ₂ CH ₃]-phenyl]	-OH	H

R ¹	R ²	R ³	R ³	R ³	R ⁶	Q = $\begin{smallmatrix} \text{C(O)NR}^2 \\ \text{R}^7 \end{smallmatrix}$
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			-(CH ₂) ₄ NHC(O)-[<i>p</i> -C(O)CH ₃]-phenyl]	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			-(CH ₂) ₄ NHC(O)- <i>p</i> -fluorophenyl	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[-C≡C-(2-pyridyl)]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[-C≡C-(<i>m</i> -hydroxyphenyl)]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -iodobenzyl	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[4-pyridyl-C(O)NH-]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[3-pyridyl-C(O)NH-]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[-NHC(O)NH- <i>m</i> -methylphenyl]-benzyl-	-OH	H

R ¹	R ²	R ³	R ⁵	R ⁶	Q = $\begin{smallmatrix} \text{C(O)NR}^2 \\ \text{R}^7 \end{smallmatrix}$
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[NHC(O)-(2,3-dihydroindol-2-yl)]- benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[di- <i>n</i> -pentylamino]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[<i>n</i> -pentylamino]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[-OCH ₂ CH ₂ N(benzyl) ₂]-benzyl	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>m</i> -hydroxybenzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[-OCH ₂ CH ₂ N(benzyl) ₂]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[CH ₂ (CH ₂) ₄ NH-]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[N- <i>n</i> -butyl, N- <i>n</i> -pentylamino]-benzyl-	-OH	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ -
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[-NHCH ₂ -(<i>p</i> -chlorophenyl)]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[-NHC(O)NH-(<i>p</i> -cyanophenyl)]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[-NHC(O)NH-(<i>p</i> -cyanophenyl)]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[-OCH ₂ COOH]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[-OCH ₂ COO- <i>i</i> -butyl]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[-OCH ₂ COO- <i>i</i> -butyl]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[-NHC(O)-5-fluoroindol-2-yl]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[-NHC(O)-(1,2,3,4-tetrahydro- isoquinolin-3-yl)]-benzyl-	-OH	H

R	R ²	R ³	R ⁵	R ⁶	Q = $\begin{matrix} \text{C}(\text{O})\text{NR}^2 \\ \text{R}^7 \end{matrix}$
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>p</i> -[-NHC(O)NH- <i>m</i> -methoxyphenyl]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>p</i> -[-NHC(O)NH- <i>m</i> -methoxyphenyl]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>p</i> -[-OCH ₂ CH ₂ -indol-3-yl]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>p</i> -[-OCH ₂ -2-(4,5-dihydro)imidazolyl]- benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>p</i> -[-NHC(O)NHCH ₂ CH ₂ CH ₃]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>p</i> -[benzylamino]benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>p</i> -[benzylamino]benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>m</i> -methoxybenzyl-	-OH	H

R ¹	R ²	R ³	R ⁵	R ⁶	Q = -C(O)NR ⁷ - R ⁷
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[-NHC(O)-pyridin-2-yl]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[-NHCH ₂ -(<i>p</i> -chlorophenyl)]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[-NHSO ₂ -CH ₂ Cl]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -(CH ₂) ₂ N-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5-dimethylthiazolidin-4-yl)		<i>p</i> -[(phenyl)C(O)NH-]benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5-dimethylthiazolidin-4-yl)		<i>p</i> -[(phenyl)C(O)NH-]benzyl-	-OH	H

R ¹	R ²	R ³	R ⁵	R ⁶	Q = $\begin{smallmatrix} \text{C(O)NR}^7 \\ \text{R}^7 \end{smallmatrix}$
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)		<i>p</i> -hydroxybenzyl-	-OCH ₂ CH ₃ ,	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>m</i> -aminobenzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>m</i> -aminobenzyl-	-OCH ₃ ,	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		2-hydroxyethyl	-OCH ₃ ,	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -nitrobenzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)		<i>p</i> -hydroxybenzyl	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -(φNHC(S)NH)benzyl-	-OH	H

R ¹	R ²	R ²	R ³	R ⁴	Q = -C(O)NR ⁷
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -(φNHC(S)NH)benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -(pyridin-3-yl-NHC(S)NH)benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -(pyridin-4-yl-CH ₂ NH)benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -(pyridin-4-yl-CH ₂ NH)benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[φCH ₂ OCH ₂ (Boc-HN)CHC(O)NH]benzyl-	-OCH ₂ φ	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		4-(pyridin-3-yl-C(O)NH)butyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		4-(pyridin-4-yl-C(O)NH)butyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ CH ₂ -C(CH ₃) ₂ - (1,4,4- dimethylpyrrolidinyl)		<i>p</i> -(pyridin-3-yl-C(O)NH)benzyl-	-OH	H

R ¹	R ²	R ³	R ³	R ³	R ⁶	Q = $\begin{smallmatrix} \text{C}(\text{O})\text{NR}^7 \\ \text{R}^7 \end{smallmatrix}$
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic -CH ₂ -CH ₂ -C(CH ₃) ₂ - (L-4,4- dimethylpyrrolidinyl)			<i>p</i> -(pyridin-4-yl-C(O)NH)benzyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)			<i>p</i> -(pyridin-3-yl-C(O)NH)benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -(pyridin-3-yl-NHC(S)NH)benzyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			4-[(<i>N</i> -toluenesulfonylpyrrolidin-2-yl)C(O)NH-]butyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			4-[(piperidin-4-yl)C(O)NH-]butyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)			<i>p</i> -(pyridin-3-yl-C(O)NH)benzyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -(2-Boc-1,2,3,4-tetrahydroisoquinolin-3-yl-NHCH ₂ -)benzyl-	-OH	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = $\begin{smallmatrix} \text{C(O)NR}^7 \\ \text{R}^7 \end{smallmatrix}$
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -(2-Boc-1,2,3,4-tetrahydroisoquinolin-3-yl- C(O)NH-)benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -(pyridin-3-yl-CH ₂ NH-)benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)			<i>p</i> -nitrobenzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -nitrobenzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[φCH ₂ O(O)C(Cbz-NH)CHCH ₂ CH ₂ - C(O)NH-]benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)			<i>p</i> -[(2-methoxyphenyl)C(O)NH-]benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)			<i>p</i> -nitrobenzyl-	-OCH ₂ CH ₃	H

R ¹	R ²	R ³	R ⁵	R ⁶	Q = -C(O)NR ⁷ -
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)		<i>p</i> -[(2-bromophenyl)C(O)NH-]benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)		<i>p</i> -[(pyrazin-2-yl)C(O)NH-]benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)		<i>p</i> -aminobenzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)		<i>p</i> -[(pyrazin-2-yl)C(O)NH-]benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)		<i>p</i> -acetamidobenzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)		<i>p</i> -[(2-methoxyphenyl)C(O)NH-]benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)		<i>p</i> -acetamidobenzyl-	-OCH ₂ CH ₃	H

R ¹	R ²	R ³	R ⁵	R ⁶	Q = $\begin{smallmatrix} \text{C(O)NR}^7 \\ \text{R}^7 \end{smallmatrix}$
<i>p</i> -CH ₃ - ϕ -	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)		<i>p</i> -acetamidobenzyl-	-OH	H
<i>p</i> -CH ₃ - ϕ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)		<i>p</i> -acetamidobenzyl-	-OCH(CH ₃) ₂	H
<i>p</i> -CH ₃ - ϕ -	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)		<i>p</i> -(pyridin-4-yl-C(O)NH)benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ - ϕ -	R ² /R ³ = cyclic -CH ₂ CH ₂ C(CH ₃) ₂ - (L-4,4- dimethylpyrrolidiny)		<i>p</i> -(1,2,3,4-tetrahydroisoquinolin-3-yl- C(O)NH-)benzyl-	-OH	H
<i>p</i> -CH ₃ - ϕ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)		<i>p</i> -(pyridin-4-yl-C(O)NH)benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ - ϕ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)		(1-toluenesulfonylimidizol-4-yl)methyl-	-OCH ₃	H

P ¹	R ²	R ³	R ⁵	R ⁶	Q = -C(O)NR ⁷ -
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)		<i>p</i> -(pyridin-3-yl-C(O)NH)benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		1-([N,N-dimethylaminosulfonyl]-imidazol-4-yl)methyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -(N,N-dimethylamino)benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -methoxybenzyl-	-OCH ₂ CH ₃	H
φ-CH ₂ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -(pyridin-4-yl-C(O)NH)benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -trifluoromethylbenzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[(2-bromophenyl)C(O)NH-]benzyl-	-OH	H

R ¹	R ²	R ³	R ⁵	R ⁶	Q = -C(O)NR ⁷ -
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[(CH ₃) ₂ NC(O)NH-]benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[CH ₃ OC(O)NH-]benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[(CH ₃) ₂ NC(O)N(CH ₃)-]benzyl-	-OCH ₂ CH ₃	H
φ-CH ₃ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -(pyridin-4-yl-C(O)NH)benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[CH ₃ OC(O)N(CH ₃)-]benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -cyanobenzyl-	-OCH ₃	H
<i>p</i> -C ₄ H ₉ -φ-	R ² /R ³ = cyclic -CH ₃ CH ₂ -SO ₂ -CH ₂ - (L-1,1- dioxothiomorpholin- 3-yl)		<i>p</i> -[(2-bromophenyl)C(O)NH-]benzyl-	-OCH ₂ CH ₃	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = $\begin{matrix} \text{C}(\text{O})\text{NR}^7 \\ \text{R}^7 \end{matrix}$
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)			<i>p</i> -cyanobenzyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic -CH ₂ CH ₂ SO ₂ -CH ₂ - (L-1,1- dioxothiomorpholin- 3-yl)			<i>p</i> -[(2-bromophenyl)C(O)NH-]benzyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)			<i>p</i> -(pyridin-4-yl)-C(O)NHbenzyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)			<i>p</i> -[(2-bromophenyl)C(O)NH-]benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)			<i>p</i> -(1,2,3,4-tetrahydroisoquinolin-3-yl- C(O)NH-)benzyl-	-OCH ₂ CH ₃	H
φ-CH ₂ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)			<i>p</i> -[(2-bromophenyl)C(O)NH-]benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)			<i>p</i> -(2-formyl-1,2,3,4-tetrahydroisoquinolin-3- yl)-C(O)NH-)benzyl-	-OCH ₃	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ -
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)			<i>p</i> -(2-formyl-1,2,3,4-tetrahydroisoquinolin-3-yl-C(O)NH-)benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ CH ₂ -SO ₂ -CH ₂ - (L-1,1-dioxothiomorpholin-3-yl)			<i>p</i> -(1,2,3,4-tetrahydroisoquinolin-3-yl-C(O)NH-)benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)			φ L-Isomer	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)			φ D-Isomer	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)			<i>p</i> -(aminomethyl)benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)			<i>p</i> -[(1-Boc-piperidin-4-yl)-C(O)NHCH ₂ -]benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)			<i>p</i> -[(1-Boc-piperidin-4-yl)-C(O)NHCH ₂ -]benzyl-	-OCH ₃	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = C(O)NR ⁷
ϕ -CH ₂ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)			<i>p</i> -(1,2,3,4-tetrahydroquinolin-3-yl)- C(O)NH-)benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₂ - ϕ -	R ² /R ³ = cyclic -CH ₂ CH ₂ -SO ₂ -CH ₂ - (L-1,1- dioxothiomorpholin- 3-yl)			<i>p</i> -(1,2,3,4-tetrahydroquinolin-2-yl)- C(O)NH-)benzyl-	-OH	H
<i>p</i> -CH ₂ - ϕ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)			<i>p</i> -[(1-Boc-piperidin-4-yl)C(O)O-]benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₂ - ϕ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)			<i>p</i> -[(piperidin-4-yl)C(O)NHCH ₂ -]benzyl-	-OH	H
<i>p</i> -CH ₂ - ϕ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)			<i>p</i> -aminobenzyl-	-OH	H
<i>p</i> -CH ₂ - ϕ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)			<i>p</i> -[(1-methylpiperidin-4-yl)-O-]benzyl-	-OCH ₂ CH ₃	H
ϕ -CH ₂ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)			<i>p</i> -(1,2,3,4-tetrahydroquinolin-2-yl)- C(O)NH-)benzyl-	-OH	H

R ¹	R ²	R ³	R ¹	R ⁶	Q = $\begin{smallmatrix} \text{C}(\text{O})\text{NR}^2 \\ \text{R}^3 \end{smallmatrix}$
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic -CH ₂ CH ₂ -SO ₂ -CH ₂ - (L-1,1- dioxothiomorpholin- 3-yl)		<i>p</i> -(pyridin-4-yl-C(O)NH)benzyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)		<i>p</i> -hydroxybenzyl-	-OCH(CH ₃) ₂	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)		<i>p</i> -hydroxybenzyl-	-OC(CH ₃) ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		α-methylbenzyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[(CH ₃) ₂ CC(O)NH-]benzyl-	-OCH(CH ₃) ₂	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[(CH ₃) ₂ CHC(O)NH-]benzyl-	-OCH(CH ₃) ₂	H

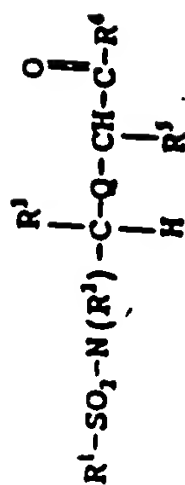
R ¹	R ²	R ³	R ⁵	R ⁶	Q = -C(O)NR ⁷
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[(CH ₃) ₂ NC(O)NH-]benzyl-	-OCH(CH ₃) ₂	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[(morpholin-4-yl)C(O)NH-]benzyl-	-OCH(CH ₃) ₂	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[(Et) ₂ NC(O)NH-]benzyl-	-OCH(CH ₃) ₂	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -hydroxybenzyl-	-OC(CH ₃) ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[(2-trifluoromethylphenyl)- C(O)NH-]benzyl-	-OCH ₂ CH ₃	H
φ-CH ₃	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5-dimethylthiazolidin- 4-yl)		<i>p</i> -hydroxybenzyl-	-OCH ₂ CH ₃	H

R ¹	R ²	R ³	R ⁵	R ⁶	Q = $\frac{-C(O)NR^7}{R^7}$
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ CH ₂ -SO ₂ -CH ₂ - (1,1,1,1-tetrathiomorpholin-3-yl)		<i>p</i> -[(morpholin-4-yl)C(O)NH-]benzyl-	-OC(CH ₃) ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[(2-methylphenyl)C(O)NH-]benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[(2-trifluoromethylphenyl)- C(O)NH-]benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		4-hydroxy-3-nitrobenzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		3-hydroxy-4-(φ-OC(O)NH-]benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[(morpholin-4-yl)C(O)NH-]benzyl-	-OC(CH ₃) ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[(thiomorpholin-4-yl)C(O)NH-]benzyl-	-OC(CH ₃) ₃	H

R ¹	R ²	R ³	R ⁵	R ⁶	Q = $\begin{smallmatrix} \text{C(O)NR}^7 \\ \text{R}^7 \end{smallmatrix}$
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[(thiomorpholin-4-yl sulfone)- C(O)NH-]benzyl-	-OC(CH ₃) ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		3-nitro-4-(CH ₃ OC(O)CH ₂ O-)benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		(2-benzoxazolinon-6-yl)methyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ CH ₂ -(Cbz)NH- CH ₂ - [L-4-N-(Cbz)- piperiziny]		<i>p</i> -hydroxybenzyl-	-OC(CH ₃) ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		(2-benzoxazolinon-6-yl)methyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		(2 <i>H</i> -1,4-benzoxazin-3(4 <i>H</i>)-one-7-yl)methyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		<i>p</i> -[(CH ₃) ₂ NS(O) ₂ N(CH ₃)-]benzyl-	-OC(CH ₃) ₃	H

R ¹	R ²	R ³	R ¹	R ⁴	Q = $\begin{smallmatrix} \text{C(O)NR}^2 \\ \text{R}^3 \end{smallmatrix}$
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)		<i>p</i> -[(2-methylpyrrolidin-1-yl)- C(O)NH-]benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)		(pyridin-4-yl)methyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)		(pyridin-4-yl)methyl-	-OH	H
<i>p</i> -F-φ	R ² /R ³ = cyclic -CH ₂ -S-CH ₂ - (L-thiazolidin-4-yl)		<i>p</i> -hydroxybenzyl-	-OC(CH ₃) ₃	H
<i>p</i> -F-φ	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (1,5,5-dimethylthiazolidin- 4-yl)		<i>p</i> -hydroxybenzyl-	-OC(CH ₃) ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)		<i>p</i> -[(1-methylpiperidin-4-yl)C(O)NH-]benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)		<i>p</i> -{[(CH ₃) ₂ NC(S)] ₂ N-}benzyl-	-OCH ₃	H

R ¹	R ²	R ³	R ⁵	R ⁶	Q = -C(O)NR ⁷ -
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>p</i> -[(CH ₃) ₂ NS(O) ₂]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>p</i> -[(CH ₃) ₂ NC(O)NH]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>p</i> -(imidazolid-2-one-1-yl)benzyl-	-OC(CH ₃) ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>p</i> -(3-formylimidazolid-2-one-1-yl)benzyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		<i>p</i> -(imidazolid-2-one-1-yl)benzyl-	-OH	H



R ¹	R ² /R ³	R ³	R ⁴	R ⁵	R ⁶	Q = C(O)NR ⁷
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		<i>p</i> -[OCH(CH ₃)φ]-benzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		<i>p</i> -hydroxybenzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		<i>p</i> -carboxybenzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		<i>m</i> -carboxybenzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		<i>p</i> -[O-(<i>o</i> -carboxyphenyl)]-benzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		<i>p</i> -benzyloxybenzyl-	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ - R ⁷
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		<i>p</i> -iodobenzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		<i>p</i> -methoxybenzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		<i>p</i> -nitrobenzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		<i>p</i> -(<i>t</i> -butoxy)benzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		(3,5-diiodo-4-hydroxyphenyl)-CH ₂ -	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		<i>p</i> -[NH ₂ C(O)φ]-benzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		(4-hydroxy-3-iodophenyl)-CH ₂ -	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		<i>p</i> -chlorobenzyl-	H

R^1	R^2	R^3	R^4	R^5	R^6	$Q = \begin{smallmatrix} C(O)NR^7 \\ R^7 \end{smallmatrix}$
$p\text{-CH}_3\text{-}\phi\text{-}$	$R^2/R^3 = \text{cyclic } 3 \text{ carbon atoms (L-pyrrolidinyl)}$		H		isobutyl-	-OH H
$p\text{-CH}_3\text{-}\phi\text{-}$	$R^2/R^3 = \text{cyclic } 3 \text{ carbon atoms (L-pyrrolidinyl)}$		H		methyl-	-OH H
$p\text{-CH}_3\text{-}\phi\text{-}$	$R^2/R^3 = \text{cyclic } 3 \text{ carbon atoms (L-pyrrolidinyl)}$		H		4-[NHC(O)CH ₃]-benzyl-	-OH H
$p\text{-CH}_3\text{-}\phi\text{-}$	$R^2/R^3 = \text{cyclic } 3 \text{ carbon atoms (L-pyrrolidinyl)}$		H		n-butyl-	-OH H
$p\text{-CH}_3\text{-}\phi\text{-}$	$R^2/R^3 = \text{cyclic } 3 \text{ carbon atoms (L-pyrrolidinyl)}$		H		CH ₃ -COOH	-OH H
$p\text{-CH}_3\text{-}\phi\text{-}$	$R^2/R^3 = \text{cyclic } 3 \text{ carbon atoms (L-pyrrolidinyl)}$		H		H ₂ N-(CH ₂) ₆ -	-OH H
$p\text{-CH}_3\text{-}\phi\text{-}$	$R^2/R^3 = \text{cyclic } 3 \text{ carbon atoms (L-pyrrolidinyl)}$		H		-CH ₂ CH ₂ -COOH	-OH H
$p\text{-CH}_3\text{-}\phi\text{-}$	$R^2/R^3 = \text{cyclic } 3 \text{ carbon atoms (L-pyrrolidinyl)}$		H		p-[di(2-benzylamino)-benzyl-	-OCH ₃ H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ - R ⁷
<i>p</i> -CH ₃ - ϕ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		H	1-N-benzylimidazol-4-yl-CH ₃	-OH	H
<i>p</i> -CH ₃ - ϕ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		H	<i>p</i> -(dibenzylamino)-benzyl-	-OH	H
<i>p</i> -CH ₃ - ϕ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		H	CH ₃ SCCH ₃ CH ₃	-OH	H
<i>p</i> -CH ₃ - ϕ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		H	HOCH ₂ -	-OH	H
<i>p</i> -CH ₃ - ϕ	R ² /R ³ = cyclic -CH ₂ -C(CH ₃) ₂ - (L-5,5'- dimethylthiazolidin- 4-yl)		H	1-N-benzylimidazol-4-yl-CH ₃	-OH	H
<i>p</i> -CH ₃ - ϕ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		H	1-N-methylimidazol-4-yl-CH ₃	-OH	H
<i>p</i> -CH ₃ - ϕ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		H	1-N-benzylimidazol-4-yl-CH ₃	-OH	H
<i>p</i> -CH ₃ - ϕ	H	-(CH ₂) ₄ COOH (L isomer)	H	<i>p</i> -hydroxybenzyl-	-OH	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = $\begin{smallmatrix} \text{C}(\text{O})\text{NR}^7 \\ \text{R}^7 \end{smallmatrix}$
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		1-N-methylimidazol-5-yl-CH ₂ -	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		3,4-(ethylenedioxy)benzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		3,4-(methylenedioxy)benzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		-CH(CH ₃) ₂	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		<i>p</i> -iodobenzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		<i>p</i> -(NHC(O)-φ)-benzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		<i>p</i> -chlorobenzyl-	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -aminobenzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[-NHIC(O)CH ₃]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ S-C(CH ₃) ₂ - (1,3,5- dimethylthiazolidin- 4-yl)		H	1-N-benzylimidazol-4-yl-CH ₂ -	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[-NHIC(O)NH- <i>m</i> -methylphenyl]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[-NHIC(O)-(2,3-dihydroindol-2-yl)]- benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[<i>n</i> -pentylamino]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[-OCH ₂ CH ₂ N(benzyl)]-benzyl	-OCH ₃	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = C(O)NR ⁷
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[OCH ₂ CH ₂ N(benzyl)]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[CH ₂ (CH ₂ NH-)-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[NHCH ₂ -(<i>p</i> -chlorophenyl)]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[NHCH(O)NH-(<i>p</i> -cyanophenyl)]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[NHCH(O)NH-(<i>p</i> -cyanophenyl)]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[OCH ₂ COO- <i>i</i> -butyl]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[OCH ₂ COO- <i>i</i> -butyl]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[NHCH(O)-(1,2,3,4-tetrahydro- isquinolin-3-yl)]-benzyl-	-OH	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = C(O)NR ⁷
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[NHIC(O)NH- <i>m</i> -methoxyphenyl]-benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[NHIC(O)NH- <i>m</i> -methoxyphenyl]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[OCH ₃ -2-(4,5-dihydroimidazolyl)-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[NHIC(O)NHCH ₂ CH ₂ CH ₃]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[benzylamino]benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[benzylamino]benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[NHCH ₃ -(<i>p</i> -chlorophenyl)]-benzyl-	-OH	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[NHISO ₂ -CH ₂ Cl]-benzyl-	-OH	H

R ¹	R ²	R ³	R ⁴	R ⁵	Q = C(O)NR ⁶
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -(CH ₃) ₂ N-benzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5'- dimethylthiazolidin- 4-yl)		H	<i>p</i> -[(phenyl)C(O)NH]-benzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5'- dimethylthiazolidin- 4-yl)		H	<i>p</i> -[(phenyl)C(O)NH]-benzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5'- dimethylthiazolidin- 4-yl)		H	<i>p</i> -hydroxybenzyl-	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5'- dimethylthiazolidin- 4-yl)		H	<i>p</i> -hydroxybenzyl	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -(pyridin-4-yl-CH ₂ NH)-benzyl-	H

R ¹	R ² /R ³	R ²	R ⁴	R ⁵	R ⁶	Q = $\text{C}(\text{O})\text{NR}^7$ R ⁷
<i>p</i> -CH ₃ - ϕ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -(pyridin-4-yl-CH ₂ NH)benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ - ϕ -	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5-dimethylthiazolidin-4-yl)		H	<i>p</i> -(pyridin-3-yl-C(O)NH)benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ - ϕ -	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5-dimethylthiazolidin-4-yl)		H	<i>p</i> -(pyridin-3-yl-C(O)NH)benzyl-	-OH	H
<i>p</i> -CH ₃ - ϕ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -(pyridin-3-yl-CH ₂ NH-)benzyl-	-OH	H
<i>p</i> -CH ₃ - ϕ -	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5-dimethylthiazolidin-4-yl)		H	<i>p</i> -nitrobenzyl-	-OCH ₃	H
<i>p</i> -CH ₃ - ϕ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -nitrobenzyl-	-OCH ₂ CH ₃	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = C(O)NR ⁷
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[(2-methoxyphenyl)C(O)NH-]benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (1,5,5-dimethylthiazolidin-4-yl)		H	<i>p</i> -nitrobenzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[(2-bromophenyl)C(O)NH-]benzyl	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[(pyrazin-2-yl)C(O)NH-]benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (1,5,5-dimethylthiazolidin-4-yl)		H	<i>p</i> -aminobenzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -acetamidobenzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[(2-methoxyphenyl)C(O)NH-]benzyl-	-OH	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = C(O)NR ⁷
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)	H	H	<i>p</i> -acetamidobenzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)	H	H	<i>p</i> -acetamidobenzyl-	-OH	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)	H	H	<i>p</i> -acetamidobenzyl-	-OCH(CH ₃) ₂	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)	H	H	<i>p</i> -(pyridin-4-yl-C(O)NH)benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)	H	H	<i>p</i> -(pyridin-4-yl-C(O)NH)benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)	H	H	(1-toluenesulfonylimidazol-4-yl)methyl-	-OCH ₃	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷
<i>p</i> -CH ₃ , φ-	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (1-5,5-dimethylthiazolidin-4-yl)		H	<i>p</i> -(pyridin-3-yl-C(O)NH)benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ , φ-	R ² /R ³ = cyclic 3 carbon atoms (1-pyrrolidinyl)		H	<i>p</i> -methoxybenzyl-	-OCH ₂ CH ₃	H
φ-CH ₃	R ² /R ³ = cyclic 3 carbon atoms (1-pyrrolidinyl)		H	<i>p</i> -(pyridin-4-yl-C(O)NH)benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ , φ-	R ² /R ³ = cyclic 3 carbon atoms (1-pyrrolidinyl)		H	<i>p</i> -[(2-bromophenyl)C(O)NH]-benzyl-	-OH	H
φ-CH ₃	R ² /R ³ = cyclic 3 carbon atoms (1-pyrrolidinyl)		H	<i>p</i> -(pyridin-4-yl-C(O)NH)benzyl-	-OH	H
<i>p</i> -CH ₃ , φ-	R ² /R ³ = cyclic -CH ₂ CH ₂ -SO ₂ -CH ₂ - (1-1,1-dioxothiomorpholin-3-yl)		H	<i>p</i> -[(2-bromophenyl)C(O)NH]-benzyl-	-OCH ₂ CH ₃	H

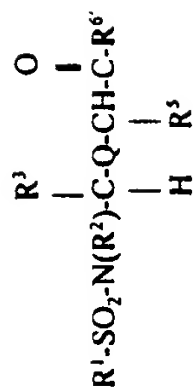
R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	Q = -C(O)NR ⁷
<i>p</i> -CH ₃ - ϕ	R ² /R ³ = cyclic -CH ₂ CH ₂ -SO ₂ -CH ₂ - (L-1,1- dioxathiomorpholin- 3-yl)		H		<i>p</i> -[(2-bromophenyl)C(O)NH]-benzyl-	-OH	H
<i>p</i> -CH ₃ - ϕ	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)		H		<i>p</i> -(pyridin-4-yl)-C(O)NH-benzyl-	-OH	H
ϕ -CH ₃ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H		<i>p</i> -[(2-bromophenyl)C(O)NH]-benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ - ϕ	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)		H		<i>p</i> -hydroxybenzyl-	-OCH(CH ₃) ₂	H
<i>p</i> -CH ₃ - ϕ	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)		H		<i>p</i> -hydroxybenzyl-	-OC(CH ₃) ₃	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -hydroxybenzyl-	-OC(CH ₃) ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[(2-trifluoromethylphenyl)- C(O)NH-]benzyl-	-OC(CH ₃)CH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[(2-methylphenyl)C(O)NH-]benzyl-	-OC(CH ₃)CH ₃	H
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		H	<i>p</i> -[(2-trifluoromethylphenyl)- C(O)NH-]benzyl-	-OH	H
<i>p</i> -H-φ	R ² /R ³ = cyclic -CH ₂ -S-CH ₂ - (L-thiazolidin-4-yl)			<i>p</i> -hydroxybenzyl-	-OC(CH ₃) ₃	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = C(O)NR ⁷
<i>p</i> -P- ϕ	R ² /R ³ = cyclic -CH ₂ -S-C(CH ₃) ₂ - (L-5,5- dimethylthiazolidin- 4-yl)		H	<i>p</i> -hydroxybenzyl-	-OC(CH ₃) ₃	H

90

TABLE 1B



R ¹	R ²	R ³	R ⁵	R ⁶	Q = -C(O)NR ⁷
p-CH ₃ -φ-	L-pyrrolidinyl		p-[nitrophenoxy carbonyloxy]-benzyl-	-OEt	H
p-CH ₃ -φ-	L-5,5-dimethyl thiazolidin- 4-yl		p-[o-bromo benzamido]- benzyl-	-Ot-Bu	H
p-CH ₃ -φ-	L-5,5-dimethyl thiazolidin-4-yl		p-[o-bromo benzamido]- benzyl-	-Ot-Bu	H
p-CH ₃ -φ-	L-pyrrolidinyl		p-[1-H-2-oxo-3-methyl tetrahydro pyrimidin-1- yl]benzyl-	-Ot-Bu	H
p-CH ₃ -φ-	L-pyrrolidinyl		p-[1-H-2-oxo-3-methyl tetrahydro pyrimidin-1- yl]benzyl-	-OH	H

R ¹	R ²	R ³	R ³	R ⁶	Q = -C(O)NR ⁷
p-CH ₃ -φ-	L-pyrrolidinyl		m-chloro-p-(t-butoxy)-benzyl-	-Ot-Bu	H
p-CH ₃ -φ-	L-pyrrolidinyl		m-chloro-p-hydroxy-benzyl-	-Ot-Bu	H
p-CH ₃ -φ-	L-pyrrolidinyl		p-[N,N-dimethyl ureido]-benzyl-	-Ot-Bu	H
p-F-φ-	L-5,5-dimethyl thiazolidin-4-yl		m-chloro-p-hydroxybenzyl-	-Ot-Bu	H
p-F-φ-	L-5,5-dimethyl thiazolidin-4-yl		m-chloro-p-hydroxybenzyl-	-Oi-Pr	H
p-CH ₃ -φ-	L-pyrrolidinyl		4-[2-methoxy phenyl]-benzyl-	-Ot-Bu	H
p-CH ₃ -φ-	L-pyrrolidinyl		4-[2-methoxy phenyl]-benzyl-	-OH	H
p-CH ₃ -φ-	L-pyrrolidinyl		5-(N,N-dimethyl ureido)-pyridin-2-yl-CH ₂ -	-OH	H
p-CH ₃ -φ-	L-pyrrolidinyl		p-[N,N-dimethyl sulfamyl]-benzyl-	-OH	H

R ¹	R ²	R ³	R ⁵	R ⁶	Q = -C(O)NR ⁷
p-CH ₃ -φ-	L-pyrrolidinyl		p-[N ¹ ,N ² ,N ² -trimethyl sulfamyl]-benzyl-	-OH	H
p-CH ₃ -φ-	L-pyrrolidinyl		1-t-butoxy carbonyl methyl imidazol-4-yl-CH ₂ -	-OMe	H
p-CH ₃ -φ-	L-pyrrolidinyl		N,N-dimethylamino carbonyl methyl imidazol-4-yl-CH ₂ -	-OMe	H
p-[N(CH ₃) ₂ C(O)-NH- φ-	L-pyrrolidinyl		p-hydroxy benzyl-	-Oi-Pr	H
p-CH ₃ -φ-	1,5,5-dimethyl thiazolidin-4-yl		m-chloro-p-hydroxybenzyl-	-Oi-Pr	H
p-CH ₃ -φ-	L-pyrrolidinyl		m-chloro-p-hydroxybenzyl-	-Oi-Pr	H
p-CH ₃ -φ-	L-pyrrolidinyl		p-carboxy methylbenzyl-	-OMe	H
p-CH ₃ -φ-	L-pyrrolidinyl		p-(2-methyl benzamido) benzyl-	-OMe	H
p-CH ₃ -φ-	L-pyrrolidinyl		p-(N,N-dimethylamino carbonyl methyl) benzyl-	-OH	H
N-1-methyl-imidazol-	L-pyrrolidinyl		p-hydroxy benzyl-	-Oi-Pr	H

R ¹	R ²	R ³	R ⁵	R ⁶	Q = -C(O)NR ⁷
p-CH ₃ -φ-	L-pyrrolidinyl		p-(2,4,5-trioxo-3-phenyl tetrahydro imidazol-1-yl)- benzyl-	-Oi-Pr	H
p-F-φ-	L-5,5-dimethyl thiazolidin- 4-yl		m-fluoro-p-hydroxybenzyl-	-Oi-Pr	H
p-F-φ-	L-5,5-dimethyl thiazolidin- 4-yl		m-chloro-p-(t-butoxy)benzyl-	-Ot-Bu	H
R ¹ /R ² / = N-[(1S)-2,10- camphor			p-hydroxy benzyl-	-Ot-Bu	H
R ¹ /R ² / = N-[(1S)-2,10- camphor		H	m-chloro-p-hydroxybenzyl-	-Oi-Pr	H
p-F-φ-	thiazolidin-4-yl	H	p-hydroxybenzyl-	-Ot-Bu	H
p-CH ₃ -φ-	L-pyrrolidinyl		p-(N,N-dimethylamino carbonyl methyl) benzyl-	-Ot-Bu	H
p-NO ₂ -φ-	L-pyrrolidinyl		p-hydroxybenzyl-	-Ot-Bu	H
p-F-φ-	L-pyrrolidinyl		p-hydroxybenzyl-	-Oi-Pr	H

R ¹	R ²	R ³	R ³	R ⁶	Q = -C(O)NR ⁷
p-F-φ-	L-5,5-dimethyl thiazolidin-4-yl		p-hydroxybenzyl-	-Ot-Bu	H
p-F-φ-	L-pyrrolidinyl		p-hydroxybenzyl-	-Oi-Pr	H
N-1-methyl-imidazol-	L-pyrrolidinyl		p-hydroxybenzyl-	-Ot-Bu	H
pyridin-3-yl	L-pyrrolidinyl		p-hydroxybenzyl-	-Ot-Bu	H
p-CH ₃ -φ-	L-pyrrolidinyl		p-(methane sulfonamido)-benzyl-	-OH	H
p-CF ₃ O-φ-	L-5,5-dimethyl thiazolidin-4-yl		p-hydroxybenzyl-	-Ot-Bu	H
p-CH ₃ -φ-	L-pyrrolidinyl		p-[2,4,5-trioxo-3-(3-chlorophenyl)-tetrahydroimidazol-1-yl]-benzyl-	-OBz	H
N-1-methyl-imidazol-	L-5,5-dimethyl thiazolidin-4-yl		m-chloro-p-hydroxybenzyl-	-OEt	H

DETAILED DESCRIPTION OF THE INVENTION

As above, this invention relates to compounds which inhibit leukocyte adhesion and, in particular, leukocyte adhesion mediated by VLA-4. However, prior to describing this invention in further detail, the following terms will first be defined.

Definitions

As used herein, "alkyl" refers to alkyl groups preferably having from 1 to 10 carbon atoms and more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, t-butyl, n-heptyl, octyl and the like.

"Substituted alkyl" refers to an alkyl group, preferably of from 1 to 10 carbon atoms, having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxylaryl, substituted aryloxyaryl, cyano, halogen, hydroxyl, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted aryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino,

-OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted
 aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-
 heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR,
 -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-
 5 substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl,
 -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-
 alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-
 substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted
 heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted
 10 heterocyclic, mono- and di-alkylamino, mono- and di-(substituted
 alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino,
 mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino,
 mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic)
 amino, unsymmetric di-substituted amines having different substituents
 15 selected from the group consisting of alkyl, substituted alkyl, aryl,
 substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and
 substituted heterocyclic; substituted alkyl groups having amino groups
 blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the
 like) and alkyl/substituted alkyl groups substituted with -SO₂-alkyl, -SO₂-
 20 substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl,
 -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-
 heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted
 heterocyclic or -SO₂NRR, where R is hydrogen or alkyl.

25 "Alkoxy" refers to the group "alkyl-O-" which includes, by way of
 example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy,
sec-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

30 "Substituted alkoxy" refers to the group "substituted alkyl-O-".

"Acyl" refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, alkynyl-C(O)-, substituted alkynyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)-, substituted heteroaryl-C(O)-, heterocyclic-C(O)-, and substituted heterocyclic-C(O)- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

10

"Acylamino" refers to the group -C(O)NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic; and where each R can be joined to form, together with the nitrogen atom, a heterocyclic or substituted heterocyclic ring wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

15
20

"Thiocarbonylamino" refers to the group -C(S)NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic, and where each R can be joined to form, together with the nitrogen atom, a heterocyclic or substituted heterocyclic ring wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted

25

cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, alkenyl-C(O)O-, substituted alkenyl-C(O)O-, alkynyl-C(O)O-, substituted alkynyl-C(O)O-, aryl-C(O)O-, substituted aryl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, heteroaryl-C(O)O-, substituted heteroaryl-C(O)O-, heterocyclic-C(O)O-, and substituted heterocyclic-C(O)O- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Alkenyl" refers to alkenyl group preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation.

"Substituted alkenyl" refers to alkenyl groups having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted

thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted
 heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy,
 substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy,
 oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-
 5 substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl,
 -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted
 heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl,
 -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-
 substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted
 10 heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl,
 -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-
 heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic,
 -NRS(O)₂-NR-substituted heterocyclic; mono- and di-alkylamino, mono- and
 di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-
 15 (substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-
 (substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and
 di-(substituted heterocyclic) amino, unsymmetric di-substituted amines
 having different substituents selected from the group consisting of alkyl,
 substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,
 20 heterocyclic and substituted heterocyclic and substituted alkenyl groups
 having amino groups blocked by conventional blocking groups (such as Boc,
 Cbz, formyl, and the like) and alkenyl/substituted alkenyl groups substituted
 with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted
 alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-
 25 substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-
 heterocyclic, -SO₂-substituted heterocyclic or -SO₂NRR, where R is
 hydrogen or alkyl.

"Alkynyl" refers to alkynyl group preferably having from 2 to 10 carbon atoms and more preferably 3 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkynyl unsaturation.

5 "Substituted alkynyl" refers to alkynyl groups having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy,
 10 aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl,
 15 guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy,
 20 substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl,
 25 -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic,
 30 -NRS(O)₂-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and

di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-
 (substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-
 (substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and
 di-(substituted heterocyclic) amino, unsymmetric di-substituted amines
 5 having different substituents selected from the group consisting of alkyl,
 substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,
 heterocyclic and substituted heterocyclic; substituted alkynyl groups having
 amino groups blocked by conventional blocking groups (such as Boc, Cbz,
 formyl, and the like), and alkynyl/substituted alkynyl groups substituted with
 10 -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl,
 -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted
 aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-
 substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl.

15 "Amidino" refers to the group $\text{H}_2\text{NC}-$ and the term "alkylamidino"

$$\begin{array}{c} \parallel \\ \text{NH} \end{array}$$

20 refers to compounds having 1 to 3 alkyl groups (e.g., alkylHNC-).

$$\begin{array}{c} \parallel \\ \text{NH} \end{array}$$

25 "Thioamidino" refers to the group $\text{RSC}-$ where R is hydrogen or

$$\begin{array}{c} \parallel \\ \text{NH} \end{array}$$

 alkyl.

"Aminoacyl" refers to the groups -NRC(O)alkyl,
 -NRC(O)substituted alkyl, -NRC(O)cycloalkyl, -NRC(O)substituted
 30 cycloalkyl, -NRC(O)alkenyl, -NRC(O)substituted alkenyl,
 -NRC(O)alkynyl, -NRC(O)substituted alkynyl, -NRC(O)aryl,
 -NRC(O)substituted aryl, -NRC(O)heteroaryl, -NRC(O)substituted
 heteroaryl, -NRC(O)heterocyclic, and -NRC(O)substituted heterocyclic,

where R is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

5

"Aminocarbonyloxy" refers to the groups -NRC(O)O-alkyl, -NRC(O)O-substituted alkyl, -NRC(O)O-alkenyl, -NRC(O)O-substituted alkenyl, -NRC(O)O-alkynyl, -NRC(O)O-substituted alkynyl, -NRC(O)O-cycloalkyl, -NRC(O)O-substituted cycloalkyl, -NRC(O)O-aryl, -NRC(O)O-substituted aryl, -NRC(O)O-heteroaryl, -NRC(O)O-substituted heteroaryl, -NRC(O)O-heterocyclic, and -NRC(O)O-substituted heterocyclic where R is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

10
15

"Oxycarbonylamino" refers to the groups -OC(O)NRR, -OC(O)NR-alkyl, -OC(O)NR-substituted alkyl, -OC(O)NR-alkenyl, -OC(O)NR-substituted alkenyl, -OC(O)NR-alkynyl, -OC(O)NR-substituted alkynyl, -OC(O)NR-cycloalkyl, -OC(O)NR-substituted cycloalkyl, -OC(O)NR-aryl, -OC(O)NR-substituted aryl, -OC(O)NR-heteroaryl, -OC(O)NR-substituted heteroaryl, -OC(O)NR-heterocyclic, and -OC(O)NR-substituted heterocyclic where R is hydrogen or alkyl, and where each R can be joined to form, together with the nitrogen atom, a heterocyclic or substituted heterocyclic ring and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

20
25

30

"Oxythiocarbonylamino" refers to the groups -OC(S)NRR,

-OC(S)NR-alkyl, -OC(S)NR-substituted alkyl, -OC(S)NR-alkenyl,
-OC(S)NR-substituted alkenyl, -OC(S)NR-alkynyl, -OC(S)NR-substituted
alkynyl, -OC(S)NR-cycloalkyl, -OC(S)NR-substituted cycloalkyl,
-OC(S)NR-aryl, -OC(S)NR-substituted aryl, -OC(S)NR-heteroaryl,
5 -OC(S)NR-substituted heteroaryl, -OC(S)NR-heterocyclic, and -OC(S)NR-
substituted heterocyclic where R is hydrogen or alkyl, or where each R can
be joined to form, together with the nitrogen atom, a heterocyclic or
substituted heterocyclic ring and wherein alkyl, substituted alkyl, alkenyl,
substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted
10 cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,
heterocyclic and substituted heterocyclic are as defined herein.

"Aminocarbonylamino" refers to the groups -NRC(O)NRR,
-NRC(O)NR-alkyl, -NRC(O)NR-substituted alkyl, -NRC(O)NR-alkenyl,
15 -NRC(O)NR-substituted alkenyl, -NRC(O)NR-alkynyl, -NRC(O)NR-
substituted alkynyl, -NRC(O)NR-aryl, -NRC(O)NR-substituted aryl,
-NRC(O)NR-cycloalkyl, -NRC(O)NR-substituted cycloalkyl, -NRC(O)NR-
heteroaryl, -NRC(O)NR-substituted heteroaryl, -NRC(O)NR-heterocyclic,
and -NRC(O)NR-substituted heterocyclic where each R is independently
20 hydrogen, alkyl, and where each R can be joined to form, together with the
nitrogen atom, a heterocyclic or substituted heterocyclic ring as well as
where one of the amino groups is blocked by conventional blocking groups
(such as Boc, Cbz, formyl, and the like) and wherein alkyl, substituted alkyl,
alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl,
25 substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted
heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminothiocabonylamino" refers to the groups -NRC(S)NRR,
-NRC(S)NR-alkyl, -NRC(S)NR-substituted alkyl, -NRC(S)NR-alkenyl,

-NRC(S)NR-substituted alkenyl, -NRC(S)NR-alkynyl, -NRC(S)NR-substituted alkynyl, -NRC(S)NR-aryl, -NRC(S)NR-substituted aryl, -NRC(S)NR-cycloalkyl, -NRC(S)NR-substituted cycloalkyl, -NRC(S)NR-heteroaryl, and -NRC(S)NR-substituted heteroaryl, -NRC(S)NR-heterocyclic, and -NRC(S)NR-substituted heterocyclic where each R is independently hydrogen, alkyl, and where each R can be joined to form, together with the nitrogen atom, a heterocyclic or substituted heterocyclic ring as well as where one of the amino groups is blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aryl" or "Ar" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl) which condensed rings may or may not be aromatic (e.g., 2-benzoxazolinone, 2H-1,4-benzoxazin-3(4H)-one-7-yl, and the like). Preferred aryls include phenyl and naphthyl.

20

Substituted aryl refers to aryl groups which are substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-

30

substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl,
 carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido,
 cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl,
 thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted
 5 thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl,
 substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl,
 substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy,
 substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy,
 heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino,
 10 oxythiocarbonylamino, -S(O)₂-alkyl, -S(O)₂-substituted alkyl, -S(O)₂-
 cycloalkyl, -S(O)₂-substituted cycloalkyl, -S(O)₂-alkenyl, -S(O)₂-substituted
 alkenyl, -S(O)₂-aryl, -S(O)₂-substituted aryl, -S(O)₂-heteroaryl, -S(O)₂-
 substituted heteroaryl, -S(O)₂-heterocyclic, -S(O)₂-substituted heterocyclic,
 -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted
 15 aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-
 heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR, -NRS(O)₂-
 alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl,
 -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-
 heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl,
 20 -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-
 substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted
 heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted
 heterocyclic, mono- and di-alkylamino, mono- and di-(substituted
 alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino,
 25 mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino,
 mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic)
 amino, unsymmetric di-substituted amines having different substituents
 selected from the group consisting of alkyl, substituted alkyl, aryl,
 substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted
 30 heterocyclic, amino groups on the substituted aryl blocked by conventional

blocking groups (such as Boc, Cbz, formyl, and the like), and -SO₂NRR, where R is hydrogen or alkyl.

"Aryloxy" refers to the group aryl-O- which includes, by way of
5 example, phenoxy, naphthoxy, and the like.

"Substituted aryloxy" refers to substituted aryl-O- groups.

"Aryloxyaryl" refers to the group -aryl-O-aryl.
10

"Substituted aryloxyaryl" refers to aryloxyaryl groups substituted with from 1 to 3 substituents on either or both aryl rings selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted
15 alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocabonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl,
20 carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted
25 thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted
30 heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino,

-S(O)₂-alkyl, -S(O)₂-substituted alkyl, -S(O)₂-cycloalkyl, -S(O)₂-substituted
 cycloalkyl, -S(O)₂-alkenyl, -S(O)₂-substituted alkenyl, -S(O)₂-aryl, -S(O)₂-
 substituted aryl, -S(O)₂-heteroaryl, -S(O)₂-substituted heteroaryl, -S(O)₂-
 heterocyclic, -S(O)₂-substituted heterocyclic, -OS(O)₂-alkyl, -OS(O)₂-
 5 substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl,
 -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted
 heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl,
 -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-
 substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted
 10 heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl,
 -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-
 heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic,
 -NRS(O)₂-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and
 di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-
 15 (substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-
 (substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and
 di-(substituted heterocyclic) amino, unsymmetric di-substituted amines
 having different substituents selected from the group consisting of alkyl,
 substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,
 20 heterocyclic and substituted heterocyclic, amino groups on the substituted
 aryl blocked by conventional blocking groups (such as Boc, Cbz, formyl, and
 the like) and substituted with -SO₂NRR, where R is hydrogen or alkyl.

"Cycloalkyl" refers to cyclic alkyl groups of from 3 to 8 carbon atoms
 25 having a single cyclic ring including, by way of example, cyclopropyl,
 cyclobutyl, cyclopentyl, cyclooctyl and the like. Excluded from this
 definition are multi-ring alkyl groups such as adamantanyl, etc.

"Cycloalkenyl" refers to cyclic alkenyl groups of from 3 to 8 carbon
 30 atoms having single or multiple unsaturation but which are not aromatic.

"Substituted cycloalkyl" and "substituted cycloalkenyl" refer to a cycloalkyl and cycloalkenyl groups, preferably of from 3 to 8 carbon atoms, having from 1 to 5 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-

(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, substituted alkynyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and alkynyl/substituted alkynyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl.

"Cycloalkoxy" refers to -O-cycloalkyl groups.

"Substituted cycloalkoxy" refers to -O-substituted cycloalkyl groups.

"Guanidino" refers to the groups -NRC(=NR)NRR, -NRC(=NR)NR-alkyl, -NRC(=NR)NR-substituted alkyl, -NRC(=NR)NR-alkenyl, -NRC(=NR)NR-substituted alkenyl, -NRC(=NR)NR-alkynyl, -NRC(=NR)NR-substituted alkynyl, -NRC(=NR)NR-aryl, -NRC(=NR)NR-substituted aryl, -NRC(=NR)NR-cycloalkyl, -NRC(=NR)NR-substituted cycloalkyl, -NRC(=NR)NR-heteroaryl, -NRC(=NR)NR-substituted heteroaryl, -NRC(=NR)NR-heterocyclic, and -NRC(=NR)NR-substituted heterocyclic where each R is independently hydrogen and alkyl as well as where one of the amino groups is blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Guanidinosulfone" refers to the groups -NRC(=NR)NRSO₂-alkyl,
-NRC(=NR)NRSO₂-substituted alkyl, -NRC(=NR)NRSO₂-alkenyl,
-NRC(=NR)NRSO₂-substituted alkenyl, -NRC(=NR)NRSO₂-alkynyl,
-NRC(=NR)NRSO₂-substituted alkynyl, -NRC(=NR)NRSO₂-aryl,
5 -NRC(=NR)NRSO₂-substituted aryl, -NRC(=NR)NRSO₂-cycloalkyl,
-NRC(=NR)NRSO₂-substituted cycloalkyl, -NRC(=NR)NRSO₂-heteroaryl,
and -NRC(=NR)NRSO₂-substituted heteroaryl, -NRC(=NR)NRSO₂-
heterocyclic, and -NRC(=NR)NRSO₂-substituted heterocyclic where each R
is independently hydrogen or alkyl and wherein alkyl, substituted alkyl,
10 alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl,
substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted
heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo and
15 preferably is either chloro or bromo.

"Heteroaryl" refers to an aromatic carbocyclic group of from 2 to 10
carbon atoms and 1 to 4 heteroatoms selected from the group consisting of
oxygen, nitrogen and sulfur within the ring. Such heteroaryl groups can have
20 a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g.,
indolizinyll or benzothienyl). Preferred heteroaryls include pyridyl, pyrrolyl,
indolyl and furyl.

"Substituted heteroaryl" refers to heteroaryl groups which are
25 substituted with from 1 to 3 substituents selected from the group consisting
of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted
alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl,
substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl,
aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryl,
30 substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted

cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy,
substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted
alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl,
carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted
5 heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic,
carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl,
substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl,
substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic,
cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro,
10 heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic,
cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted
heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy,
oxycarbonylamino, oxythiocarbonylamino, -S(O)₂-alkyl, -S(O)₂-substituted
alkyl, -S(O)₂-cycloalkyl, -S(O)₂-substituted cycloalkyl, -S(O)₂-alkenyl,
15 -S(O)₂-substituted alkenyl, -S(O)₂-aryl, -S(O)₂-substituted aryl, -S(O)₂-
heteroaryl, -S(O)₂-substituted heteroaryl, -S(O)₂-heterocyclic, -S(O)₂-
substituted heterocyclic, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-
aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted
heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-
20 NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl,
-NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted
heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic,
-NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl,
-NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-
25 substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted
heterocyclic, mono- and di-alkylamino, mono- and di-(substituted
alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino,
mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino,
mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic)
30 amino, unsymmetric di-substituted amines having different substituents

selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, amino groups on the substituted aryl blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like), and
5 -SO₂NRR, where R is hydrogen or alkyl.

"Heteroaryloxy" refers to the group -O-heteroaryl and "substituted heteroaryloxy" refers to the group -O-substituted heteroaryl.

10 "Heterocycle" or "heterocyclic" refers to a saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur or oxygen within the ring wherein, in fused ring systems, one or more the rings can be aryl or heteroaryl.

15 "Saturated heterocyclic" refers to heterocycles of single or multiple condensed rings lacking unsaturation in any ring (e.g., carbon to carbon unsaturation, carbon to nitrogen unsaturation, nitrogen to nitrogen unsaturation, and the like).

20 "Unsaturated heterocyclic" refers to non-aromatic heterocycles of single or multiple condensed rings having unsaturation in any ring (e.g., carbon to carbon unsaturation, carbon to nitrogen unsaturation, nitrogen to nitrogen unsaturation, and the like).

25 "Substituted heterocyclic" refers to heterocycle groups which are substituted with from 1 to 3 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino,
30 aminoacyl, aminocarbonylamino, aminothiocabonylamino,

aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy,
 aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro,
 carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl,
 carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl,
 5 carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic,
 carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl,
 guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl,
 substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl,
 thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted
 10 thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted
 heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy,
 substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy,
 oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-
 substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl,
 15 -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted
 heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl,
 -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-
 substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted
 heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl,
 20 -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-
 heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic,
 -NRS(O)₂-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and
 di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-
 (substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-
 25 (substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and
 di-(substituted heterocyclic) amino, unsymmetric di-substituted amines
 having different substituents selected from the group consisting of alkyl,
 substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,
 heterocyclic and substituted heterocyclic, substituted alkynyl groups having
 30 amino groups blocked by conventional blocking groups (such as Boc, Cbz,

formyl, and the like) and alkynyl/substituted alkynyl groups substituted with
-SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl,
-SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted
aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-
5 substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl.

Examples of heterocycles and heteroaryls include, but are not limited
to, azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine,
pyridazine, indolizine, isoindole, indole, dihydroindole, indazole, purine,
10 quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine,
quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline,
phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole,
phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine,
piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-
15 tetrahydrobenzo[b]thiophene, thiazole, thiazolidine, thiophene,
benzo[b]thiophene, morpholino, thiomorpholino, piperidiny, pyrrolidine,
tetrahydrofuranyl, and the like.

"Saturated substituted heterocyclic" refers to substituted heterocycles
20 of single or multiple condensed rings lacking unsaturation in any ring (e.g.,
carbon to carbon unsaturation, carbon to nitrogen unsaturation, nitrogen to
nitrogen unsaturation, and the like).

"Unsaturated substituted heterocyclic" refers to non-aromatic
25 substituted heterocycles of single or multiple condensed rings having
unsaturation in any ring (e.g., carbon to carbon unsaturation, carbon to
nitrogen unsaturation, nitrogen to nitrogen unsaturation, and the like).

"Heterocyclyloxy" refers to the group -O-heterocyclic and
30 "substituted heterocyclyloxy" refers to the group -O-substituted heterocyclic.

"Thiol" refers to the group -SH.

"Thioalkyl" refers to the groups -S-alkyl.

5 "Substituted thioalkyl" refers to the group -S-substituted alkyl.

"Thiocycloalkyl" refers to the groups -S-cycloalkyl.

10 "Substituted thiocycloalkyl" refers to the group -S-substituted cycloalkyl.

"Thioaryl" refers to the group -S-aryl and "substituted thioaryl" refers to the group -S-substituted aryl.

15 "Thioheteroaryl" refers to the group -S-heteroaryl and "substituted thioheteroaryl" refers to the group -S-substituted heteroaryl.

20 "Thioheterocyclic" refers to the group -S-heterocyclic and "substituted thioheterocyclic" refers to the group -S-substituted heterocyclic.

25 "Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts of a compound of Formula I or Formula IA, which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound (of Formula I or IA) contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

30

Compound Preparation

The compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

10

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

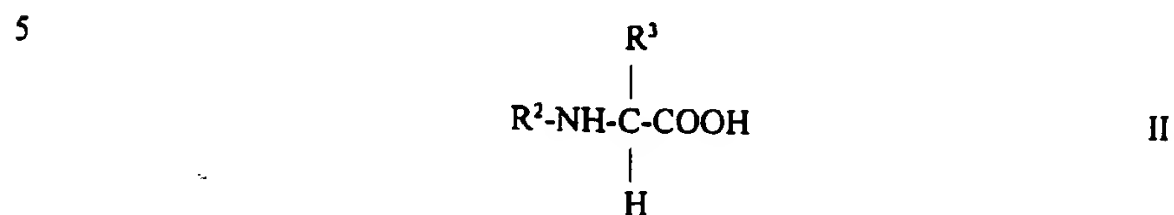
15

Furthermore, the compounds of this invention will typically contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this invention, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

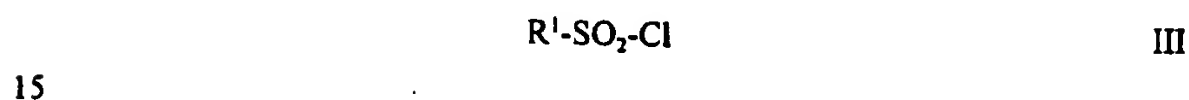
25

30

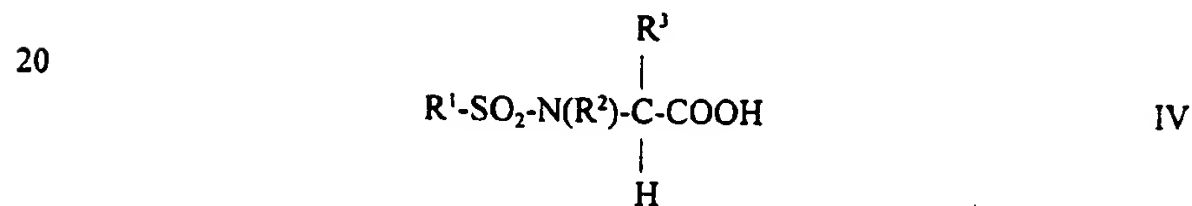
In a preferred method of synthesis, the compounds of formula I and IA wherein Q is $-\text{C}(\text{O})\text{NR}^7-$ are prepared by first coupling an amino acid of formula II:



wherein R^2 and R^3 are as defined above, with a sulfonyl chloride of formula III:



wherein R^1 is as defined above, to provide an *N*-sulfonyl amino acid of formula IV:



wherein $\text{R}^1\text{-R}^3$ are as defined above.

This reaction is typically conducted by contacting the amino acid of formula II with at least one equivalent, preferably about 1.1 to about 2 equivalents, of sulfonyl chloride III in an inert diluent such as dichloromethane and the like. Generally, the reaction is conducted at a temperature ranging from about -70°C to about 40°C for about 1 to about 24 hours. Preferably, this reaction is conducted in the presence of a suitable

base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like, as the base. Upon completion of the reaction, the resulting *N*-sulfonyl amino acid IV is recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, and the like.

The amino acids of formula II employed in the above reaction are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. Examples of suitable amino acids for use in this reaction include, but are not limited to, L-proline, *trans*-4-hydroxyl-L-proline, *cis*-4-hydroxyl-L-proline, *trans*-3-phenyl-L-proline, *cis*-3-phenyl-L-proline, L-(2-methyl)proline, L-pipecolinic acid, L-azetidine-2-carboxylic acid, glycine, 2-*tert*-butylglycine, D,L-phenylglycine, L-alanine, α -methylalanine, *N*-methyl-L-phenylalanine, L-diphenylalanine, sarcosine, D,L-phenylsarcosine, L-aspartic acid β -*tert*-butyl ester, L-glutamic acid γ -*tert*-butyl ester, L-(*O*-benzyl)serine, 1-aminocyclopropanecarboxylic acid, 1-aminocyclobutanecarboxylic acid, 1-aminocyclopentanecarboxylic acid (cycloleucine) 1-aminocyclo-hexanecarboxylic acid, L-serine and the like. If desired, the corresponding carboxylic acid esters of the amino acids of formula II, such as the methyl esters, ethyl esters and the like, can be employed in the above reaction with the sulfonyl chloride III. Subsequent hydrolysis of the ester group to the carboxylic acid using conventional reagents and conditions, i.e., treatment with an alkali metal hydroxide in an inert diluent such as methanol/water, then provides the *N*-sulfonyl amino acid IV.

Similarly, the sulfonyl chlorides of formula III employed in the above reaction are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. Such compounds are typically prepared from the corresponding sulfonic acid, i.e.,
5 from compounds of the formula R^1-SO_3H where R^1 is as defined above, using phosphorous trichloride and phosphorous pentachloride. This reaction is generally conducted by contacting the sulfonic acid with about 2 to 5 molar equivalents of phosphorous trichloride and phosphorous pentachloride, either neat or in an inert solvent, such as dichloromethane, at temperature in
10 the range of about $0^\circ C$ to about $80^\circ C$ for about 1 to about 48 hours to afford the sulfonyl chloride. Alternatively, the sulfonyl chlorides of formula III can be prepared from the corresponding thiol compound, i.e., from compounds of the formula R^1-SH where R^1 is as defined above, by treating the thiol with chlorine (Cl_2) and water under conventional reaction conditions.

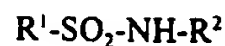
15

Examples of sulfonyl chlorides suitable for use in this invention include, but are not limited to, methanesulfonyl chloride, 2-propanesulfonyl chloride, 1-butanesulfonyl chloride, benzenesulfonyl chloride, 1-naphthalenesulfonyl chloride, 2-naphthalenesulfonyl chloride,
20 *p*-toluenesulfonyl chloride, α -toluenesulfonyl chloride, 4-acetamidobenzenesulfonyl chloride, 4-amidinobenzenesulfonyl chloride, 4-*tert*-butylbenzenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, 2-carboxybenzenesulfonyl chloride, 4-cyanobenzenesulfonyl chloride, 3,4-dichlorobenzenesulfonyl chloride, 3,5-dichlorobenzenesulfonyl chloride, 3,4-dimethoxybenzenesulfonyl chloride, 3,5-ditrifluoromethylbenzenesulfonyl
25 chloride, 4-fluorobenzenesulfonyl chloride, 4-methoxybenzenesulfonyl chloride, 2-methoxycarbonylbenzenesulfonyl chloride, 4-methylamidobenzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride, 4-thioamidobenzenesulfonyl chloride, 4-trifluoromethylbenzenesulfonyl
30 chloride, 4-trifluoromethoxybenzenesulfonyl chloride, 2,4,6-

trimethylbenzenesulfonyl chloride, 2-phenylethanesulfonyl chloride,
2-thiophenesulfonyl chloride, 5-chloro-2-thiophenesulfonyl chloride, 2,5-
dichloro-4-thiophenesulfonyl chloride, 2-thiazolesulfonyl chloride, 2-methyl-
4-thiazolesulfonyl chloride, 1-methyl-4-imidazolesulfonyl chloride,
5 1-methyl-4-pyrazolesulfonyl chloride, 5-chloro-1,3-dimethyl-4-
pyrazolesulfonyl chloride, 3-pyridinesulfonyl chloride, 2-pyrimidinesulfonyl
chloride, and the like. If desired, a sulfonyl fluoride, sulfonyl bromide or
sulfonic acid anhydride may be used in place of the sulfonyl chloride in the
above reaction to form the *N*-sulfonyl amino acids of formula IV.

10

The intermediate *N*-sulfonyl amino acids of formula IV, wherein R³
is hydrogen, can also be prepared by reacting a sulfonamide of formula V:



V

15

wherein R¹ and R² are as defined above, with a carboxylic acid derivative of
the formula L(R³)CHCOOR where L is a leaving group, such as chloro,
bromo, iodo, mesylate, tosylate and the like, R³ is as defined above and R is
hydrogen or an alkyl group. This reaction is typically conducted by
20 contacting the sulfonamide V with at least one equivalent, preferably 1.1 to 2
equivalents, of the carboxylic acid derivative in the presence of a suitable
base, such as triethylamine, in an inert diluent, such as DMF, at a
temperature ranging from about 24°C to about 37°C for about 0.5 to about 4
hours. This reaction is further described in Zuckermann et al., *J. Am. Chem.*
25 *Soc.*, 1992, 114, 10646-10647. Preferred carboxylic acid derivatives for use
in this reaction are α -chloro and α -bromocarboxylic acid esters such as *tert*-
butyl bromoacetate, and the like. When an carboxylic acid ester is employed
in this reaction, the ester group is subsequently hydrolyzed using
conventional procedures to afford an *N*-sulfonyl amino acid of formula IV.

30

The compounds of formula I and IA are then prepared by coupling the intermediate *N*-sulfonyl amino acid of formula IV with an amino acid derivative of formula VI:



wherein R^5 - R^7 are as defined above. This coupling reaction is typically conducted using well-known coupling reagents such as carbodiimides, BOP reagent (benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate) and the like. Suitable carbodiimides include, by way of example, dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and the like. If desired, polymer supported forms of carbodiimide coupling reagents may also be used including, for example, those described in *Tetrahedron Letters*, 34(48), 7685 (1993). Additionally, well-known coupling promoters, such as *N*-hydroxysuccinimide, 1-hydroxybenzotriazole and the like, may be used to facilitate the coupling reaction.

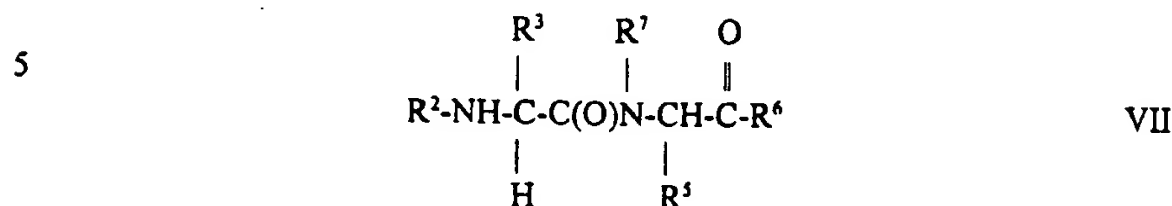
This coupling reaction is typically conducted by contacting the *N*-sulfonylamino acid IV with about 1 to about 2 equivalents of the coupling reagent and at least one equivalent, preferably about 1 to about 1.2 equivalents, of amino acid derivative VI in an inert diluent, such as dichloromethane, chloroform, acetonitrile, tetrahydrofuran, *N,N*-dimethylformamide and the like. Generally, this reaction is conducted at a temperature ranging from about 0°C to about 37°C for about 12 to about 24 hours. Upon completion of the reaction, the compound of formula I is

recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, and the like.

Alternatively, the *N*-sulfonyl amino acid IV can be converted into an acid halide and the acid halide coupled with amino acid derivative VI to provide compounds of formula I. The acid halide of VI can be prepared by contacting VI with an inorganic acid halide, such as thionyl chloride, phosphorous trichloride, phosphorous tribromide or phosphorous pentachloride, or preferably, with oxalyl chloride under conventional conditions. Generally, this reaction is conducted using about 1 to 5 molar equivalents of the inorganic acid halide or oxalyl chloride, either neat or in an inert solvent, such as dichloromethane or carbon tetrachloride, at a temperature in the range of about 0°C to about 80°C for about 1 to about 48 hours. A catalyst, such as *N,N*-dimethylformamide, may also be used in this reaction.

The acid halide of *N*-sulfonyl amino acid IV is then contacted with at least one equivalent, preferably about 1.1 to about 1.5 equivalents, of amino acid derivative VI in an inert diluent, such as dichloromethane, at a temperature ranging from about -70°C to about 40°C for about 1 to about 24 hours. Preferably, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylnmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like. Upon completion of the reaction, the compound of formula I is recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, and the like.

Alternatively, the compounds of formula I can be prepared by first forming a diamino acid derivative of formula VII:



wherein R², R³, R⁵, R⁶, and R⁷ are as defined above. The diamino acid derivatives of formula VII can be readily prepared by coupling an amino acid of formula II with an amino acid derivative of formula VI using conventional amino acid coupling techniques and reagents, such carbodiimides, BOP reagent and the like, as described above. Diamino acid VII can then be sulfonated using a sulfonyl chloride of formula III and using the synthetic procedures described above to provide a compound of formula I.

The amino acid derivatives of formula VI employed in the above reactions are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. For example, amino acid derivatives of formula VI can be prepared by C-alkylating commercially available diethyl 2-acetamidomalonate (Aldrich, Milwaukee, Wisconsin, USA) with an alkyl or substituted alkyl halide. This reaction is typically conducted by treating the diethyl 2-acetamidomalonate with at least one equivalent of sodium ethoxide and at least one equivalent of an alkyl or substituted alkyl halide in refluxing ethanol for about 6 to about 12 hours. The resulting C-alkylated malonate is then deacetylated, hydrolyzed and decarboxylated by heating in aqueous hydrochloric acid at reflux for about 6 to about 12 hours to provide the amino acid, typically as the hydrochloride salt.

Examples of amino acid derivatives of formula VI suitable for use in the above reactions include, but are not limited to, L-alanine methyl ester, L-isoleucine methyl ester, L-leucine methyl ester, L-valine methyl ester, β -*tert*-butyl-L-aspartic acid methyl ester, L-asparagine *tert*-butyl ester, ϵ -Boc-L-lysine methyl ester, ϵ -Cbz-L-lysine methyl ester, γ -*tert*-butyl-L-glutamic acid methyl ester, L-glutamine *tert*-butyl ester, L-(*N*-methyl)histidine methyl ester, L-(*N*-benzyl)histidine methyl ester, L-methionine methyl ester, L-(*O*-benzyl)serine methyl ester, L-tryptophan methyl ester, L-phenylalanine methyl ester, L-phenylalanine isopropyl ester, L-phenylalanine benzyl ester, L-phenylalaninamide, *N*-methyl-L-phenylalanine benzyl ester, 3-carboxy-D,L-phenylalanine methyl ester, 4-carboxy-D,L-phenylalanine methyl ester, L-4-chlorophenylalanine methyl ester, L-4-(3-dimethylaminopropoxy)phenylalanine methyl ester, L-4-iodophenylalanine methyl ester, L-3,4-methylenedioxyphenylalanine methyl ester, L-3,4-ethylenedioxyphenylalanine methyl ester, L-4-nitrophenylalanine methyl ester, L-tyrosine methyl ester, D,L-homophenylalanine methyl ester, L-(*O*-methyl)tyrosine methyl ester, L-(*O-tert*-butyl)tyrosine methyl ester, L-(*O*-benzyl)tyrosine methyl ester, L-3,5-diiodotyrosine methyl ester, L-3-iodotyrosine methyl ester, β -(1-naphthyl)-L-alanine methyl ester, β -(2-naphthyl)-L-alanine methyl ester, β -(2-thienyl)-L-alanine methyl ester, β -cyclohexyl-L-alanine methyl ester, β -(2-pyridyl)-L-alanine methyl ester, β -(3-pyridyl)-L-alanine methyl ester, β -(4-pyridyl)-L-alanine methyl ester, β -(2-thiazolyl)-D,L-alanine methyl ester, β -(1,2,4-triazol-3-yl)-D,L-alanine methyl ester, and the like. If desired, of course, other esters or amides of the above-described compounds may also be employed.

For ease of synthesis, the compounds of formula I are typically prepared as an ester, i.e., where R⁶ is an alkoxy or substituted alkoxy group and the like. If desired, the ester group can be hydrolysed using conventional conditions and reagents to provide the corresponding carboxylic acid.

Typically, this reaction is conducted by treating the ester with at least one equivalent of an alkali metal hydroxide, such as lithium, sodium or potassium hydroxide, in an inert diluent, such as methanol or mixtures of methanol and water, at a temperature ranging about 0°C to about 24°C for about 1 to about 12 hours. Alternatively, benzyl esters may be removed by hydrogenolysis using a palladium catalyst, such as palladium on carbon. The resulting carboxylic acids may be coupled, if desired, to amines such as β -alanine ethyl ester, hydroxyamines such as hydroxylamine and *N*-hydroxysuccinimide, alkoxyamines and substituted alkoxyamines such as *O*-methylhydroxylamine and *O*-benzylhydroxylamine, and the like, using conventional coupling reagents and conditions as described above.

As will be apparent to those skilled in the art, other functional groups present on any of the substituents of the compounds of formula I can be readily modified or derivatized either before or after the above-described coupling reactions using well-known synthetic procedures. For example, a nitro group present on a substituent of a compound of formula I or an intermediate thereof may be readily reduced by hydrogenation in the presence of a palladium catalyst, such as palladium on carbon, to provide the corresponding amino group. This reaction is typically conducted at a temperature of from about 20°C to about 50°C for about 6 to about 24 hours in an inert diluent, such as methanol. Compounds having a nitro group on the R⁵ substituent can be prepared, for example, by using a 4-nitrophenylalanine derivative and the like in the above-described coupling reactions.

Similarly, a pyridyl group can be hydrogenated in the presence of a platinum catalyst, such as platinum oxide, in an acidic diluent to provide the corresponding piperidinyl analogue. Generally, this reaction is conducted by treating the pyridine compound with hydrogen at a pressure ranging from

about 20 psi to about 60 psi, preferably about 40 psi, in the presence of the catalyst at a temperature of about 20°C to about 50°C for about 2 to about 24 hours in an acidic diluent, such as a mixture of methanol and aqueous hydrochloric acid. Compounds having a pyridyl group can be readily
5 prepared by using, for example, β -(2-pyridyl)-, β -(3-pyridyl)- or β -(4-pyridyl)-L-alanine derivatives in the above-described coupling reactions.

Additionally, when the R⁵ substituent of a compound of formula I or an intermediate thereof contains a primary or secondary amino group, such
10 amino groups can be further derivatized either before or after the above coupling reactions to provide, by way of example, amides, sulfonamides, ureas, thioureas, carbamates, secondary or tertiary amines and the like. Compounds having a primary amino group on the R⁵ substituent may be prepared, for example, by reduction of the corresponding nitro compound as
15 described above. Alternatively, such compounds can be prepared by using an amino acid derivative of formula VI derived from lysine, 4-aminophenylalanine and the like in the above-described coupling reactions.

By way of illustration, a compound of formula I or an intermediate
20 thereof having a substituent containing a primary or secondary amino group, such as where R⁵ is a (4-aminophenyl)methyl group, can be readily *N*-acylated using conventional acylating reagents and conditions to provide the corresponding amide. This acylation reaction is typically conducted by treating the amino compound with at least one equivalent, preferably about
25 1.1 to about 1.2 equivalents, of a carboxylic acid in the presence of a coupling reagent such as a carbodiimide, BOP reagent (benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate) and the like, in an inert diluent, such as dichloromethane, chloroform, acetonitrile, tetrahydrofuran, *N,N*-dimethylformamide and the like, at a temperature
30 ranging from about 0°C to about 37°C for about 4 to about 24 hours.

Preferably, a promoter, such as *N*-hydroxysuccinimide, 1-hydroxy-benzotriazole and the like, is used to facilitate the acylation reaction.

Examples of carboxylic acids suitable for use in this reaction include, but are not limited to, *N*-*tert*-butyloxycarbonylglycine, *N*-*tert*-butyloxycarbonyl-L-phenylalanine, *N*-*tert*-butyloxycarbonyl-L-aspartic acid benzyl ester, benzoic acid, *N*-*tert*-butyloxycarbonylisonipecotic acid, *N*-methylisonipecotic acid, *N*-*tert*-butyloxycarbonylnipecotic acid, *N*-*tert*-butyloxycarbonyl-L-tetrahydroisoquinoline-3-carboxylic acid, *N*-(toluene-4-sulfonyl)-L-proline and the like.

10

Alternatively, a compound of formula I or an intermediate thereof containing a primary or secondary amino group can be *N*-acylated using an acyl halide or a carboxylic acid anhydride to form the corresponding amide. This reaction is typically conducted by contacting the amino compound with at least one equivalent, preferably about 1.1 to about 1.2 equivalents, of the acyl halide or carboxylic acid anhydride in an inert diluent, such as dichloromethane, at a temperature ranging from about -70°C to about 40°C for about 1 to about 24 hours. If desired, an acylation catalyst such as 4-(*N,N*-dimethylamino)pyridine may be used to promote the acylation reaction. The acylation reaction is preferably conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like.

20
25

Examples of acyl halides and carboxylic acid anhydrides suitable for use in this reaction include, but are not limited to, 2-methylpropionyl chloride, trimethylacetyl chloride, phenylacetyl chloride, benzoyl chloride, 2-bromobenzoyl chloride, 2-methylbenzoyl chloride, 2-trifluoro-

30

methylbenzoyl chloride, isonicotinoyl chloride, nicotinoyl chloride, picolinoyl chloride, acetic anhydride, succinic anhydride, and the like. Carbamyl chlorides, such as *N,N*-dimethylcarbamyl chloride, *N,N*-diethylcarbamyl chloride and the like, can also be used in this reaction to provide ureas. Similarly, dicarbonates, such as di-*tert*-butyl dicarbonate, may be employed to provide carbamates.

In a similar manner, a compound of formula I or an intermediate thereof containing a primary or secondary amino group may be *N*-sulfonated to form a sulfonamide using a sulfonyl halide or a sulfonic acid anhydride. Sulfonyl halides and sulfonic acid anhydrides suitable for use in this reaction include, but are not limited to, methanesulfonyl chloride, chloromethanesulfonyl chloride, *p*-toluenesulfonyl chloride, trifluoromethanesulfonic anhydride, and the like. Similarly, sulfamoyl chlorides, such as dimethylsulfamoyl chloride, can be used to provide sulfamides (e.g., >N-SO₂-N<).

Additionally, a primary and secondary amino group present on a substituent of a compound of formula I or an intermediate thereof can be reacted with an isocyanate or a thioisocyanate to give a urea or thiourea, respectively. This reaction is typically conducted by contacting the amino compound with at least one equivalent, preferably about 1.1 to about 1.2 equivalents, of the isocyanate or thioisocyanate in an inert diluent, such as toluene and the like, at a temperature ranging from about 24°C to about 37°C for about 12 to about 24 hours. The isocyanates and thioisocyanates used in this reaction are commercially available or can be prepared from commercially available compounds using well-known synthetic procedures. For example, isocyanates and thioisocyanates are readily prepared by reacting the appropriate amine with phosgene or thiophosgene. Examples of isocyanates and thioisocyanates suitable for use in this reaction include, but

are not limited to, ethyl isocyanate, *n*-propyl isocyanate, 4-cyanophenyl isocyanate, 3-methoxyphenyl isocyanate, 2-phenylethyl isocyanate, methyl thioisocyanate, ethyl thioisocyanate, 2-phenylethyl thioisocyanate, 3-phenylpropyl thioisocyanate, 3-(*N,N*-diethylamino)propyl thioisocyanate, 5 phenyl thioisocyanate, benzyl thioisocyanate, 3-pyridyl thioisocyanate, fluorescein isothiocyanate (isomer I) and the like.

Furthermore, when a compound of formula I or IA, or an intermediate thereof, contains a primary or secondary amino group, the 10 amino group can be reductively alkylated using aldehydes or ketones to form a secondary or tertiary amino group. This reaction is typically conducted by contacting the amino compound with at least one equivalent, preferably about 1.1 to about 1.5 equivalents, of an aldehyde or ketone and at least one equivalent based on the amino compound of a metal hydride reducing agent, 15 such as sodium cyanoborohydride, in an inert diluent, such as methanol, tetrahydrofuran, mixtures thereof and the like, at a temperature ranging from about 0°C to about 50°C for about 1 to about 72 hours. Aldehydes and ketones suitable for use in this reaction include, by way of example, benzaldehyde, 4-chlorobenzaldehyde, valeraldehyde and the like.

20

In a similar manner, when a compound of formula I or an intermediate thereof has a substituent containing a hydroxyl group, the hydroxyl group can be further modified or derivatized either before or after the above coupling reactions to provide, by way of example, ethers, 25 carbamates and the like. Compounds having a hydroxyl group on the R⁵ substituent, for example, can be prepared using an amino acid derivative of formula VI derived from tyrosine and the like in the above-described reactions.

By way of example, a compound of formula I or an intermediate thereof having a substituent containing a hydroxyl group, such as where R⁵ is a (4-hydroxyphenyl)methyl group, can be readily *O*-alkylated to form ethers. This *O*-alkylation reaction is typically conducted by contacting the hydroxy
5 compound with a suitable alkali or alkaline earth metal base, such as potassium carbonate, in an inert diluent, such as acetone, 2-butanone and the like, to form the alkali or alkaline earth metal salt of the hydroxyl group. This salt is generally not isolated, but is reacted *in situ* with at least one equivalent of an alkyl or substituted alkyl halide or sulfonate, such as an
10 alkyl chloride, bromide, iodide, mesylate or tosylate, to afford the ether. Generally, this reaction is conducted at a temperature ranging from about 60°C to about 150°C for about 24 to about 72 hours. Preferably, a catalytic amount of sodium or potassium iodide is added to the reaction mixture when an alkyl chloride or bromide is employed in the reaction.

15

Examples of alkyl or substituted alkyl halides and sulfonates suitable for use in this reaction include, but are not limited to, *tert*-butyl bromoacetate, *N-tert*-butyl chloroacetamide, 1-bromoethylbenzene, ethyl α -bromophenylacetate, 2-(*N*-ethyl-*N*-phenylamino)ethyl chloride, 2-(*N,N*-ethylamino)ethyl chloride, 2-(*N,N*-diisopropylamino)ethyl chloride, 2-(*N,N*-dibenzylamino)ethyl chloride, 3-(*N,N*-ethylamino)propyl chloride, 3-(*N*-benzyl-*N*-methylamino)propyl chloride, *N*-(2-chloroethyl)morpholine, 2-(hexamethyleneimino)ethyl chloride, 3-(*N*-methylpiperazine)propyl chloride, 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine, 2-(4-hydroxy-4-phenylpiperidine)ethyl chloride, *N-tert*-butyloxycarbonyl-3-piperidinemethyl
25 tosylate, and the like.

Alternatively, a hydroxyl group present on a substituent of a compound of formula I or an intermediate thereof can be *O*-alkylating using
30 the Mitsunobu reaction. In this reaction, an alcohol, such as 3-(*N,N*-

dimethylamino)-1-propanol and the like, is reacted with about 1.0 to about 1.3 equivalents of triphenylphosphine and about 1.0 to about 1.3 equivalents of diethyl azodicarboxylate in an inert diluent, such as tetrahydrofuran, at a temperature ranging from about -10°C to about 5°C for about 0.25 to about 1 hour. About 1.0 to about 1.3 equivalents of a hydroxy compound, such as *N-tert*-butyltyrosine methyl ester, is then added and the reaction mixture is stirred at a temperature of about 0°C to about 30°C for about 2 to about 48 hours to provide the *O*-alkylated product.

10 In a similar manner, a compound of formula I or an intermediate thereof containing a aryl hydroxy group can be reacted with an aryl iodide to provide a diaryl ether. Generally, this reaction is conducted by forming the alkali metal salt of the hydroxyl group using a suitable base, such as sodium hydride, in an inert diluent such as xylenes at a temperature of about -25°C to about 10°C. The salt is then treated with about 1.1 to about 1.5 equivalents of cuprous bromide dimethyl sulfide complex at a temperature ranging from about 10°C to about 30°C for about 0.5 to about 2.0 hours, followed by about 1.1 to about 1.5 equivalents of an aryl iodide, such as sodium 2-iodobenzoate and the like. The reaction is then heated to about 70°C to about 150°C for about 2 to about 24 hours to provide the diaryl ether.

Additionally, a hydroxy-containing compound can also be readily derivatized to form a carbamate. In one method for preparing such carbamates, a hydroxy compound of formula I or an intermediate thereof is contacted with about 1.0 to about 1.2 equivalents of 4-nitrophenyl chloroformate in an inert diluent, such as dichloromethane, at a temperature ranging from about -25°C to about 0°C for about 0.5 to about 2.0 hours. Treatment of the resulting carbonate with an excess, preferably about 2 to about 5 equivalents, of a trialkylamine, such as triethylamine, for about 0.5

to 2 hours, followed by about 1.0 to about 1.5 equivalents of a primary or secondary amine provides the carbamate. Examples of amines suitable for using in this reaction include, but are not limited to, piperazine, 1-methylpiperazine, 1-acetylpiperazine, morpholine, thiomorpholine,
5 pyrrolidine, piperidine and the like.

Alternatively, in another method for preparing carbamates, a hydroxy-containing compound is contacted with about 1.0 to about 1.5 equivalents of a carbamyl chloride in an inert diluent, such as
10 dichloromethane, at a temperature ranging from about 25°C to about 70°C for about 2 to about 72 hours. Typically, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like.
15 Additionally, at least one equivalent (based on the hydroxy compound) of 4-(*N,N*-dimethylamino)pyridine is preferably added to the reaction mixture to facilitate the reaction. Examples of carbamyl chlorides suitable for use in this reaction include, by way of example, dimethylcarbamyl chloride, diethylcarbamyl chloride and the like.

20

Likewise, when a compound of formula I or an intermediate thereof contains a primary or secondary hydroxyl group, such hydroxyl groups can be readily converted into a leaving group and displaced to form, for example, amines, sulfides and fluorides. For example, derivatives of 4-hydroxy-L-
25 proline can be converted into the corresponding 4-amino, 4-thio or 4-fluoro-L-proline derivatives via nucleophilic displacement of the derivatized hydroxyl group. Generally, when a chiral compound is employed in these reactions, the stereochemistry at the carbon atom attached to the derivatized hydroxyl group is inverted.

30

These reactions are typically conducted by first converting the hydroxyl group into a leaving group, such as a tosylate, by treatment of the hydroxy compound with at least one equivalent of a sulfonyl halide, such as *p*-toluenesulfonyl chloride and the like, in pyridine. This reaction is
5 generally conducted at a temperature of from about 0°C to about 70°C for about 1 to about 48 hours. The resulting tosylate can then be readily displaced with sodium azide, for example, by contacting the tosylate with at least one equivalent of sodium azide in an inert diluent, such as a mixture of *N,N*-dimethylformamide and water, at a temperature ranging from about 0°C
10 to about 37°C for about 1 to about 12 hours to provide the corresponding azido compound. The azido group can then be reduced by, for example, hydrogenation using a palladium on carbon catalyst to provide the amino (-NH₂) compound.

15 Similarly, a tosylate group can be readily displaced by a thiol to form a sulfide. This reaction is typically conducted by contacting the tosylate with at least one equivalent of a thiol, such as thiophenol, in the presence of a suitable base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), in an inert diluent, such as *N,N*-dimethylformamide, at a temperature of from about 0°C
20 to about 37°C for about 1 to about 12 hours to provide the sulfide. Additionally, treatment of a tosylate with morpholinosulfur trifluoride in an inert diluent, such as dichloromethane, at a temperature ranging from about 0°C to about 37°C for about 12 to about 24 hours affords the corresponding fluoro compound.

25 Furthermore, a compound of formula I or IA or an intermediate thereof having a substituent containing an iodoaryl group, for example, when R⁵ is a (4-iodophenyl)methyl group, can be readily converted either before or after the above coupling reactions into a biaryl compound. Typically, this
30 reaction is conducted by treating the iodoaryl compound with about 1.1 to

about 2 equivalents of an arylzinc iodide, such as 2-(methoxycarbonyl)-phenylzinc iodide, in the presence of a palladium catalyst, such as palladium tetra(triphenylphosphine), in an inert diluent, such as tetrahydrofuran, at a temperature ranging from about 24°C to about 30°C until reaction completion. This reaction is further described, for example, in Rieke, *J. Org. Chem.* 1991, 56, 1445.

In some cases, the compounds of formula I or IA or intermediates thereof may contain substituents having one or more sulfur atoms. Such sulfur atoms will be present, for example, when the amino acid of formula II employed in the above reactions is derived from L-thiazolidine-4-carboxylic acid, L-(5,5-dimethyl)thiazolidine-4-carboxylic acid, L-thiamorpholine-3-carboxylic acid and the like. When present, such sulfur atoms can be oxidized either before or after the above coupling reactions to provide a sulfoxide or sulfone compound using conventional reagents and reaction conditions. Suitable reagents for oxidizing a sulfide compound to a sulfoxide include, by way of example, hydrogen peroxide, 3-chloroperoxybenzoic acid (MCPBA), sodium periodate and the like. The oxidation reaction is typically conducted by contacting the sulfide compound with about 0.95 to about 1.1 equivalents of the oxidizing reagent in an inert diluent, such as dichloromethane, at a temperature ranging from about -50°C to about 75°C for about 1 to about 24 hours. The resulting sulfoxide can then be further oxidized to the corresponding sulfone by contacting the sulfoxide with at least one additional equivalent of an oxidizing reagent, such as hydrogen peroxide, MCPBA, potassium permanganate and the like. Alternatively, the sulfone can be prepared directly by contacting the sulfide with at least two equivalents, and preferably an excess, of the oxidizing reagent. Such reactions are described further in March, "Advanced Organic Chemistry", 4th Ed., pp. 1201-1202, Wiley Publisher, 1992.

As described above, the compounds of formula I having an R² substituent other than hydrogen can be prepared using an *N*-substituted amino acid of formula II, such as sarcosine, *N*-methyl-L-phenylalanine and the like, in the above-described coupling reactions. Alternatively, such compounds
5 can be prepared by *N*-alkylation of a sulfonamide of formula I or IV (where R² is hydrogen) using conventional synthetic procedures. Typically, this *N*-alkylation reaction is conducted by contacting the sulfonamide with at least one equivalent, preferably 1.1 to 2 equivalents, of an alkyl or substituted alkyl halide in the presence of a suitable base, such as potassium carbonate,
10 in an inert diluent, such as acetone, 2-butanone and the like, at a temperature ranging from about 25°C to about 70°C for about 2 to about 48 hours. Examples of alkyl or substituted alkyl halides suitable for use in this reaction include, but are not limited to, methyl iodide, and the like.

15 Additionally, the sulfonamides of formula I or IV wherein R² is hydrogen and R¹ is a 2-alkoxycarbonylaryl group can be intramolecularly cyclized to form 1,2-benzisothiazol-3-one derivatives or analogues thereof. This reaction is typically conducted by treating a sulfonamide, such as *N*-(2-methoxycarbonylphenylsulfonyl)glycine-L-phenylalanine benzyl ester, with
20 about 1.0 to 1.5 equivalents of a suitable base, such as an alkali metal hydride, in an inert diluent, such as tetrahydrofuran, at a temperature ranging from about 0°C to about 30°C for about 2 to about 48 hours to afford the cyclized 1,2-benzisothiazol-3-one derivative.

25 Lastly, the compounds of formula I where Q is -C(S)NR⁷- can be prepared by using an amino thionoacid derivative in place of amino acid II in the above described synthetic procedures. Such amino thionoacid derivatives can be prepared by the procedures described in Shalaky, et al., *J. Org. Chem.*, 61:9045-9048 (1996) and Brain, et al., *J. Org. Chem.*, 62:3808-3809
30 (1997) and references cited therein.

Pharmaceutical Formulations

When employed as pharmaceuticals, the compounds of formula I and IA are usually administered in the form of pharmaceutical compositions.

5 These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and include at least one active compound.

10 This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of formula I and IA above associated with pharmaceutically acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a
15 carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions,
20 solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

25 In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally

adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose,
5 sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and
10 suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

15

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects
20 and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compound is effective over a wide dosage range and is
25 generally administered in a pharmaceutically effective amount. It, will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the
30 individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can include an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*.

5 Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent

10 positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The following formulation examples illustrate the pharmaceutical

15 compositions of the present invention.

Formulation Example 1

Hard gelatin capsules containing the following ingredients are prepared:

20	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
	Active Ingredient	30.0
	Starch	305.0
25	Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Formulation Example 2

A tablet formula is prepared using the ingredients below:

5	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/tablet)</u>
	Active Ingredient	25.0
	Cellulose, microcrystalline	200.0
	Colloidal silicon dioxide	10.0
10	Stearic acid	5.0

The components are blended and compressed to form tablets, each weighing 240 mg.

Formulation Example 3

15 A dry powder inhaler formulation is prepared containing the following components:

20	<u>Ingredient</u>	<u>Weight %</u>
	Active Ingredient	5
	Lactose	95

The active mixture is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

25 Formulation Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

30	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/tablet)</u>
	Active Ingredient	30.0 mg
	Starch	45.0 mg
	Microcrystalline cellulose	35.0 mg
	Polyvinylpyrrolidone (as 10% solution in water)	4.0 mg
35	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
	Talc	<u>1.0 mg</u>
	Total	120 mg

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

10

Formulation Example 5

Capsules, each containing 40 mg of medicament are made as follows:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
15	Active Ingredient	40.0 mg
	Starch	109.0 mg
	Magnesium stearate	<u>1.0 mg</u>
	Total	150.0 mg

20

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

25

Formulation Example 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

	<u>Ingredient</u>	<u>Amount</u>
30	Active Ingredient	25 mg
	Saturated fatty acid glycerides to	2,000 mg

35

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

5

Formulation Example 7

Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

	<u>Ingredient</u>	<u>Amount</u>
10	Active Ingredient	50.00mg
	Xanthan gum	4.00mg
	Sodium carboxymethyl cellulose (11%)	
	Microcrystalline cellulose (89%)	50.00mg
15	Sucrose	1.75 g
	Sodium benzoate	10.00mg
	Flavor and Color	q.v.
	Purified water to	5.00ml

20

The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

25

Formulation Example 8

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
30	Active Ingredient	15.0 mg
	Starch	407.0 mg
	Magnesium stearate	<u>3.0 mg</u>
35	Total	425.0 mg

5

An intravenous formulation may be prepared as follows:

10

A topical formulation may be prepared as follows:

15

25

30

patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

It may be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system used for the transport of biological factors to specific anatomical regions of the body is described in U.S. Patent 5,011,472 which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

Utility

The compounds of this invention can be employed to bind VLA-4 ($\alpha_4\beta_1$ integrin) in biological samples and, accordingly have utility in, for example, assaying such samples for VLA-4. In such assays, the compounds can be bound to a solid support and the VLA-4 sample added thereto. The amount of VLA-4 in the sample can be determined by conventional methods such as use of a sandwich ELISA assay. Alternatively, labeled VLA-4 can be used in a competitive assay to measure for the presence of VLA-4 in the sample. Other suitable assays are well known in the art.

In addition, certain of the compounds of this invention inhibit, *in vivo*, adhesion of leukocytes to endothelial cells mediated by VLA-4 and, accordingly, can be used in the treatment of diseases mediated by VLA-4. Such diseases include inflammatory diseases in mammalian patients
5 such as asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetes), inflammatory bowel disease (including ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, atopic
10 dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

The biological activity of the compounds identified above may be assayed in a variety of systems. For example, a compound can be
15 immobilized on a solid surface and adhesion of cells expressing VLA-4 can be measured. Using such formats, large numbers of compounds can be screened. Cells suitable for this assay include any leukocytes known to express VLA-4 such as T cells, B cells, monocytes, eosinophils, and basophils. A number of leukocyte cell lines can also be used, examples
20 include Jurkat and U937.

The test compounds can also be tested for the ability to competitively inhibit binding between VLA-4 and VCAM-1, or between VLA-4 and a labeled compound known to bind VLA-4 such as a compound of this
25 invention or antibodies to VLA-4. In these assays, the VCAM-1 can be immobilized on a solid surface. VCAM-1 may also be expressed as a recombinant fusion protein having an Ig tail (e.g., IgG) so that binding to VLA-4 may be detected in an immunoassay. Alternatively, VCAM-19 expressing cells, such as activated endothelial cells or VCAM-1 transfected
30 fibroblasts can be used. For assays to measure the ability to block adhesion

to brain endothelial cells, the assays described in International Patent Application Publication No. WO 91/05038 are particularly preferred. This application is incorporated herein by reference in its entirety.

5 Many assay formats employ labelled assay components. The labelling systems can be in a variety of forms. The label may be coupled directly or indirectly to the desired component of the assay according to methods well known in the art. A wide variety of labels may be used. The component may be labelled by any one of several methods. The most
10 common method of detection is the use of autoradiography with ^3H , ^{125}I , ^{35}S , ^{14}C , or ^{32}P labelled compounds and the like. Non-radioactive labels include ligands which bind to labelled antibodies, fluorophores, chemiluminescent agents, enzymes and antibodies which can serve as specific binding pair members for a labelled ligand. The choice of label depends on sensitivity
15 required, ease of conjugation with the compound, stability requirements, and available instrumentation.

 Appropriate *in vivo* models for demonstrating efficacy in treating inflammatory responses include EAE (experimental autoimmune
20 encephalomyelitis) in mice, rats, guinea pigs or primates, as well as other inflammatory models dependent upon $\alpha 4$ integrins.

 Compounds having the desired biological activity may be modified as necessary to provide desired properties such as improved pharmacological
25 properties (e.g., *in vivo* stability, bio-availability), or the ability to be detected in diagnostic applications. For instance, inclusion of one or more D-amino acids in the sulfonamides of this invention typically increases *in vivo* stability. Stability can be assayed in a variety of ways such as by measuring the half-life of the proteins during incubation with peptidases or
30 human plasma or serum. A number of such protein stability assays have

been described (see, e.g., Verhoef et al., *Eur. J. Drug Metab. Pharmacokinet.*, 1990, 15(2):83-93).

For diagnostic purposes, a wide variety of labels may be linked to the compounds, which may provide, directly or indirectly, a detectable signal. Thus, the compounds of the subject invention may be modified in a variety of ways for a variety of end purposes while still retaining biological activity. In addition, various reactive sites may be introduced at the terminus for linking to particles, solid substrates, macromolecules, and the like.

Labeled compounds can be used in a variety of *in vivo* or *in vitro* applications. A wide variety of labels may be employed, such as radionuclides (e.g., gamma-emitting radioisotopes such as technetium-99 or indium-111), fluorescers (e.g., fluorescein), enzymes, enzyme substrates, enzyme cofactors, enzyme inhibitors, chemiluminescent compounds, bioluminescent compounds, and the like. Those of ordinary skill in the art will know of other suitable labels for binding to the complexes, or will be able to ascertain such using routine experimentation. The binding of these labels is achieved using standard techniques common to those of ordinary skill in the art.

In vitro uses include diagnostic applications such as monitoring inflammatory responses by detecting the presence of leukocytes expressing VLA-4. The compounds of this invention can also be used for isolating or labeling such cells. In addition, as mentioned above, the compounds of the invention can be used to assay for potential inhibitors of VLA-4/VCAM-1 interactions.

For *in vivo* diagnostic imaging to identify, e.g., sites of inflammation, radioisotopes are typically used in accordance with well known techniques.

The radioisotopes may be bound to the peptide either directly or indirectly using intermediate functional groups. For instance, chelating agents such as diethylenetriaminepentacetic acid (DTPA) and ethylenediaminetetraacetic acid (EDTA) and similar molecules have been used to bind proteins to
5 metallic ion radioisotopes.

The complexes can also be labeled with a paramagnetic isotope for purposes of *in vivo* diagnosis, as in magnetic resonance imaging (MRI) or electron spin resonance (ESR), both of which are well known. In general,
10 any conventional method for visualizing diagnostic images can be used. Usually gamma- and positron-emitting radioisotopes are used for camera imaging and paramagnetic isotopes are used for MRI. Thus, the compounds can be used to monitor the course of amelioration of an inflammatory response in an individual. By measuring the increase or decrease in
15 lymphocytes expressing VLA-4 it is possible to determine whether a particular therapeutic regimen aimed at ameliorating the disease is effective.

The pharmaceutical compositions of the present invention can be used to block or inhibit cellular adhesion associated with a number of
20 diseases and disorders, or to treat diseases in a mammalian patient which are mediated by $\alpha_v\beta_1$. For instance, a number of inflammatory disorders are associated with integrins or leukocytes. Treatable disorders include, e.g., transplantation rejection (e.g., allograft rejection), Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset
25 diabetes), retinitis, cancer metastases, rheumatoid arthritis, acute leukocyte-mediated lung injury (e.g., adult respiratory distress syndrome), asthma, nephritis, and acute and chronic inflammation, including atopic dermatitis, psoriasis, myocardial ischemia, and inflammatory bowel disease (including Crohn's disease and ulcerative colitis). In preferred embodiments

the pharmaceutical compositions are used to treat inflammatory brain disorders, such as multiple sclerosis (MS), viral meningitis and encephalitis.

Inflammatory bowel disease is a collective term for two similar
5 diseases referred to as Crohn's disease and ulcerative colitis. Crohn's disease is an idiopathic, chronic ulceroinflammatory disease characterized by sharply delimited and typically transmural involvement of all layers of the bowel wall by a granulomatous inflammatory reaction. Any
10 segment of the gastrointestinal tract, from the mouth to the anus, may be involved, although the disease most commonly affects the terminal ileum and/or colon. Ulcerative colitis is an inflammatory response limited largely to the colonic mucosa and submucosa. Lymphocytes and macrophages are numerous in lesions of inflammatory bowel disease and may contribute to inflammatory injury.

15

Asthma is a disease characterized by increased responsiveness of the tracheobronchial tree to various stimuli potentiating paroxysmal constriction of the bronchial airways. The stimuli cause release of various mediators of inflammation from IgE-coated mast cells including histamine, eosinophilic
20 and neutrophilic chemotactic factors, leukotrienes, prostaglandin and platelet activating factor. Release of these factors recruits basophils, eosinophils and neutrophils, which cause inflammatory injury.

Atherosclerosis is a disease of arteries (e.g., coronary, carotid, aorta
25 and iliac). The basic lesion, the atheroma, consists of a raised focal plaque within the intima, having a core of lipid and a covering fibrous cap. Atheromas compromise arterial blood flow and weaken affected arteries. Myocardial and cerebral infarcts are a major consequence of this disease. Macrophages and leukocytes are recruited to atheromas and contribute to
30 inflammatory injury.

Rheumatoid arthritis is a chronic, relapsing inflammatory disease that primarily causes impairment and destruction of joints. Rheumatoid arthritis usually first affects the small joints of the hands and feet but then may involve the wrists, elbows, ankles and knees. The arthritis results from
5 interaction of synovial cells with leukocytes that infiltrate from the circulation into the synovial lining of the joints. See *e.g.*, Paul, *Immunology* (3d ed., Raven Press, 1993).

Another indication for the compounds of this invention is in
10 treatment of organ or graft rejection mediated by VLA-4. Over recent years there has been a considerable improvement in the efficiency of surgical techniques for transplanting tissues and organs such as skin, kidney, liver, heart, lung, pancreas and bone marrow. Perhaps the principal outstanding
15 problem is the lack of satisfactory agents for inducing immunotolerance in the recipient to the transplanted allograft or organ. When allogeneic cells or organs are transplanted into a host (*i.e.*, the donor and donee are different individuals from the same species), the host immune system is likely to mount an immune response to foreign antigens in the transplant (host-versus-graft disease) leading to destruction of the transplanted tissue. CD8⁺ cells,
20 CD4 cells and monocytes are all involved in the rejection of transplant tissues. Compounds of this invention which bind to alpha-4 integrin are useful, *inter alia*, to block alloantigen-induced immune responses in the donee thereby preventing such cells from participating in the destruction of the transplanted tissue or organ. See, *e.g.*, Paul et al., *Transplant*
25 *International* 9, 420-425 (1996); Georczynski et al., *Immunology* 87, 573-580 (1996); Georczynski et al., *Transplant. Immunol.* 3, 55-61 (1995); Yang et al., *Transplantation* 60, 71-76 (1995); Anderson et al., *APMIS* 102, 23-27 (1994).

A related use for compounds of this invention which bind to VLA-4 is in modulating the immune response involved in "graft versus host" disease (GVHD). See *e.g.*, Schlegel et al., *J. Immunol.* 155, 3856-3865 (1995). GVHD is a potentially fatal disease that occurs when immunologically
5 competent cells are transferred to an allogeneic recipient. In this situation, the donor's immunocompetent cells may attack tissues in the recipient. Tissues of the skin, gut epithelia and liver are frequent targets and may be destroyed during the course of GVHD. The disease presents an especially severe problem when immune tissue is being transplanted, such as in bone
10 marrow transplantation; but less severe GVHD has also been reported in other cases as well, including heart and liver transplants. The therapeutic agents of the present invention are used, *inter alia*, to block activation of the donor T-cells thereby interfering with their ability to lyse target cells in the host.

15

A further use of the compounds of this invention is inhibiting tumor metastasis. Several tumor cells have been reported to express VLA-4 and compounds which bind VLA-4 block adhesion of such cells to endothelial cells. Steinback et al., *Urol. Res.* 23, 175-83 (1995); Orosz et al., *Int. J.*
20 *Cancer* 60, 867-71 (1995); Freedman et al., *Leuk. Lymphoma* 13, 47-52 (1994); Okahara et al., *Cancer Res.* 54, 3233-6 (1994).

A further use of the compounds of this invention is in treating multiple sclerosis. Multiple sclerosis is a progressive neurological
25 autoimmune disease that affects an estimated 250,000 to 350,000 people in the United States. Multiple sclerosis is thought to be the result of a specific autoimmune reaction in which certain leukocytes attack and initiate the destruction of myelin, the insulating sheath covering nerve fibers. In an animal model for multiple sclerosis, murine monoclonal antibodies directed
30 against VLA-4 have been shown to block the adhesion of leukocytes to the

endothelium, and thus prevent inflammation of the central nervous system and subsequent paralysis in the animals¹⁶.

Pharmaceutical compositions of the invention are suitable for use in a
5 variety of drug delivery systems. Suitable formulations for use in the present invention are found in *Remington's Pharmaceutical Sciences*, Mace Publishing Company, Philadelphia, PA, 17th ed. (1985).

In order to enhance serum half-life, the compounds may be
-10 encapsulated, introduced into the lumen of liposomes, prepared as a colloid, or other conventional techniques may be employed which provide an extended serum half-life of the compounds. A variety of methods are available for preparing liposomes, as described in, e.g., Szoka, et al., U.S. Patent Nos. 4,235,871, 4,501,728 and 4,837,028 each of which is
15 incorporated herein by reference.

The amount administered to the patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration,
20 and the like. In therapeutic applications, compositions are administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as "therapeutically effective dose." Amounts effective for this use will depend on the disease condition
25 being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the inflammation, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient are in the form of
30 pharmaceutical compositions described above. These compositions may be

sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound
5 preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

10 The therapeutic dosage of the compounds of the present invention will vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. For example, for intravenous administration, the dose will typically be in the
15 range of about 20 μg to about 500 μg per kilogram body weight, preferably about 100 μg to about 300 μg per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.1 μg to 1 mg per kilogram body weight. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

20

The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention. Unless otherwise stated, all temperatures are in degrees Celsius.

25

EXAMPLES

In the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

30

aq or aq. = aqueous

	AcOH	=	acetic acid
	bd	=	broad doublet
	bm	=	broad multiplet
	bs	=	broad singlet
5	Bn	=	benzyl
	Boc	=	<i>N</i> - <i>tert</i> -butoxycarbonyl
	Boc ₂ O	=	di- <i>tert</i> -butyl dicarbonate
	BOP	=	benzotriazol-1-yloxy-
10			tris(dimethylamino)phosphonium
			hexafluorophosphate
	Cbz	=	carbobenzyloxy
	CHCl ₃	=	chloroform
	CH ₂ Cl ₂	=	dichloromethane
	(COCl) ₂	=	oxalyl chloride
15	d	=	doublet
	dd	=	doublet of doublets
	dt	=	doublet of triplets
	DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
	DCC	=	1,3-dicyclohexylcarbodiimide
20	DMAP	=	4- <i>N,N</i> -dimethylaminopyridine
	DME	=	ethylene glycol dimethyl ether
	DMF	=	<i>N,N</i> -dimethylformamide
	DMSO	=	dimethylsulfoxide
	EDC	=	1-(3-dimethylaminopropyl)-3-
25			ethylcarbodiimide hydrochloride
	Et ₃ N	=	triethylamine
	Et ₂ O	=	diethyl ether
	EtOAc	=	ethyl acetate
	EtOH	=	ethanol
30	eq or eq.	=	equivalent
	Fmoc	=	<i>N</i> -(9-fluorenylmethoxycarbonyl)
	FmocONSu	=	<i>N</i> -(9-fluorenylmethoxycarbonyl)-
			succinimide
35	g	=	grams
	h	=	hour
	H ₂ O	=	water
	HBr	=	hydrobromic acid
	HCl	=	hydrochloric acid
	HOBT	=	1-hydroxybenzotriazole hydrate
40	hr	=	hour
	K ₂ CO ₃	=	potassium carbonate
	L	=	liter
	m	=	multiplet
	MeOH	=	methanol

	mg	=	milligram
	MgSO ₄	=	magnesium sulfate
	mL	=	milliliter
	mm	=	millimeter
5	mM	=	millimolar
	mmol	=	millimol
	mp	=	melting point
	N	=	normal
	NaCl	=	sodium chloride
10	Na ₂ CO ₃	=	sodium carbonate
	NaHCO ₃	=	sodium bicarbonate
	NaOEt	=	sodium ethoxide
	NaOH	=	sodium hydroxide
	NH ₄ Cl	=	ammonium chloride
15	NMM	=	<i>N</i> -methylmorpholine
	Phe	=	L-phenylalanine
	Pro	=	L-proline
	psi	=	pounds per square inch
	PtO ₂	=	platinum oxide
20	q	=	quartet
	quint.	=	quintet
	rt	=	room temperature
	s	=	singlet
	sat	=	saturated
25	t	=	triplet
	t-BuOH	=	<i>tert</i> -butanol
	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran
	TLC or tlc	=	thin layer chromatography
30	Ts	=	tosyl
	TsCl	=	tosyl chloride
	TsOH	=	tosylate
	μL	=	microliter

35

In the examples below, all temperatures are in degrees Celcius (unless otherwise indicated). The following Methods were used to prepare the compounds set forth below as indicated.

Method 1

N-Tosylation Procedure

N-Tosylation of the appropriate amino acid was conducted via the method of Cupps, Boutin and Rapoport *J. Org. Chem.* 1985, 50, 3972.

5

Method 2

Methyl Ester Preparation Procedure

Amino acid methyl esters were prepared using the method of Brenner and Huber *Helv. Chim. Acta* 1953, 36, 1109.

10

Method 3

BOP Coupling Procedure

The desired dipeptide esters were prepared by the reaction of a suitable N-protected amino acid (1 equivalent) with the appropriate amino acid ester or amino acid ester hydrochloride (1 equivalent), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate [BOP] (2.0 equivalent), triethylamine (1.1 equivalent), and DMF. The reaction mixture was stirred at room temperature overnight. The crude product was purified flash chromatography to afford the dipeptide ester.

15
20

Method 4

Hydrogenation Procedure I

Hydrogenation was performed using 10% palladium on carbon (10% by weight) in methanol at 30 psi overnight. The reaction mixtures were filtered through a pad of Celite and the filtrate concentrated to yield the desired amino compounds.

25

Method 5

Hydrolysis Procedure I

To a chilled (0°C) THF/H₂O solution (2:1, 5 - 10 mL) of the appropriate ester was added LiOH (or NaOH) (0.95 equivalents). The temperature was maintained at 0°C and the reaction was complete in 1 to 3 hours. The reaction mixture was extracted with ethyl acetate and the aqueous phase was lyophilized resulting in the desired carboxylate salt.

Method 6

Ester Hydrolysis Procedure II

To a chilled (0°C) THF/H₂O solution (2:1, 5 - 10 mL) of the appropriate ester was added LiOH (1.1 equivalents). The temperature was maintained at 0°C and the reaction was complete in 1 to 3 hours. The reaction mixture was concentrated and the residue was taken up into H₂O and the pH adjusted to 2 to 3 with aqueous HCl. The product was extracted with ethyl acetate and the combined organic phase was washed with brine, dried over MgSO₄, filtered and concentrated to yield the desired acid.

Method 7

Ester Hydrolysis Procedure III

The appropriate ester was dissolved in dioxane/H₂O (1:1) and 0.9 equivalents of 0.5 N NaOH was added. The reaction was stirred for 3 to 16 hours and then concentrated. The resulting residue was dissolved in H₂O and extracted with ethyl acetate. The aqueous phase was lyophilized to yield the desired carboxylate sodium salt.

Method 8

Sulfonylation Procedure I

To the appropriately protected amino acid analog (11.2 mmol), dissolved in methylene chloride (25ml) and cooled to -78°C was added the

desired sulfonyl chloride (12 mmol) followed by dropwise addition of pyridine (2 mL). The solution was allowed to warm to room temperature and was stirred for 48 hr. The reaction solution was transferred to a 250 mL separatory funnel with methylene chloride (100 mL) and extracted with 1N HCl (50 mL x 3), brine (50 mL), and water (100 mL). The organic phase was dried (MgSO₄) and the solvent concentrated to yield the desired product.

Method 9

Reductive Amination Procedure

Reductive amination of Tos-Pro-p-NH₂-Phe with the appropriate aldehyde was conducted using acetic acid, sodium triacetoxyborohydride, methylene chloride and the combined mixture was stirred at room temperature overnight. The crude product was purified by flash chromatography.

Method 10

BOC Removal Procedure

Anhydrous hydrochloride (HCl) gas was bubbled through a methanolic solution of the appropriate Boc-amino acid ester at 0°C for 15 minutes and the reaction mixture was stirred for three hours. The solution was concentrated to a syrup and dissolved in Et₂O and reconcentrated. This procedure was repeated and the resulting solid was placed under high vacuum overnight.

Method 11

Tert-Butyl Ester Hydrolysis Procedure I

The *tert*-butyl ester was dissolved in CH₂Cl₂ and treated with TFA. The reaction was complete in 1-3 hr at which time the reaction mixture was concentrated and the residue dissolved in H₂O and lyophilized to yield the desired acid.

Method 12

EDC Coupling Procedure I

To a CH_2Cl_2 solution (5-20 mL) of N-(toluene-4-sulfonyl)-L-proline (1 equivalent), the appropriate amino acid ester hydrochloride (1 equivalent),
5 N-methylmorpholine (1.1-2.2 equivalents) and 1-hydroxybenzotriazole (2 equivalents) were mixed, placed in an ice bath and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (1.1 equivalents) was added. The reaction was allowed to rise to room temperature and stirred overnight. The reaction mixture was poured into H_2O and the organic phase was washed
10 with sat. NaHCO_3 , brine, dried (MgSO_4 or Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography.

Method 13

EDC Coupling Procedure II

15 To a DMF solution (5-20 mL) of the appropriate N-protected amino acid (1 equivalent), the appropriated amino acid ester hydrochloride (1 equivalent), Et_3N (1.1 equivalents) and 1-hydroxybenzotriazole (2 equivalents) were mixed, placed in an ice bath and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (1.1 equivalents) was added.
20 The reaction was allowed to rise to room temperature and stirred overnight. The reaction mixture was partitioned between EtOAc and H_2O and the organic phase washed with 0.2 N citric acid, H_2O , sat. NaHCO_3 , and brine, then dried (MgSO_4 or Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography or preparative TLC.

25

Method 14

Sulfonylation Procedure II

The appropriate sulfonyl chloride was dissolved in CH_2Cl_2 and placed in an ice bath. L-Pro-L-Phe-OMe • HCl (1 equivalent) and Et_3N

(1.1 equivalent) was added and the reaction allowed to warm to room temperature and stirred overnight under an atmosphere of nitrogen. The reaction mixture was concentrated and the residue partitioned between EtOAc and H₂O and the organic phase washed with sat. NaHCO₃, brine, dried (MgSO₄ or Na₂SO₄), filtered and concentrated. The crude product was purified by column chromatography or preparative TLC.

Method 15

Sulfonylation Procedure III

To a solution of L-Pro-L-4-(3-dimethylaminopropoxy)-Phe-OMe [prepared using the procedure described in Method 10] (1 equivalent) in CH₂Cl₂ was added Et₃N (5 equivalents) followed by the appropriate sulfonyl chloride (1.1 equivalent). The reaction was allowed to warm to room temperature and stirred overnight under an atmosphere of nitrogen. The mixture was concentrated, dissolved in EtOAc, washed with sat. NaHCO₃ and 0.2 N citric acid. The aqueous phase was made basic with solid NaHCO₃ and the product extracted with EtOAc. The organic phase was washed with brine, dried (MgSO₄ or Na₂SO₄), filtered and concentrated. The crude methyl ester was purified by preparative TLC. The corresponding acid was prepared using the procedure described in Method 7.

Method 16

Hydrogenation Procedure II

To a methanol (10 -15 mL) solution of the azlactone was added NaOAc (1 equivalent) and 10% Pd/C. This mixture was placed on the hydrogenator at 40 psi H₂. After 8 - 16 hours, the reaction mixture was filtered through a pad of Celite and the filtrate concentrated to yield the dehydrodipeptide methyl ester. The ester was dissolved in dioxane/H₂O (5-10 mL), to which was added 0.5 N NaOH (1.05 equivalents). After stirring for 1- 3 hours, the reaction mixture was concentrated and the residue was

redissolved in H₂O and washed with EtOAc. The aqueous phase was made acidic with 0.2 N HCl and the product was extracted with EtOAc. The combined organic phase was washed with brine (1 x 5 mL), dried (MgSO₄ or Na₂SO₄), filtered and concentrated to yield the acid as approximately a 1:1 mixture of diastereomers.

Method 17

Tert-Butyl Ester Hydrolysis Procedure II

The *tert*-butyl ester was dissolved in CH₂Cl₂ (5 mL) and treated with TFA (5 mL). The reaction was complete in 1-3 hours at which time the reaction mixture was concentrated and the residue dissolved in H₂O and concentrated. The residue was redissolved in H₂O and lyophilized to yield the desired product.

Example 1

15

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-4-(α -methylbenzyloxy)-L-phenylalanine

N-(Toluene-4-sulfonyl)-L-prolyl-L-tyrosine methyl ester (see Example 2 (3)) (785 mg, 1.89 mmol) was dissolved in DMF (20 mL) at room temperature. To this was added K₂CO₃ (1.1 eq, 281 mg) and 1-bromoethyl benzene (1.1 eq, 284 μ L). The reaction was stirred for 12 hours at room temperature. Ethyl acetate (100 mL) was added, and the organic layer washed several times with brine (5 x 50 mL). The organic layer was dried over MgSO₄. Upon filtration and evaporation of the solvents under reduced pressure, an oil was isolated. The crude material was purified by elution on silica gel (EtOAc/hexanes (1:4)). The desired material was isolated in 32% yield (330 mg, 0.6 mmol). The methyl ester (330 mg, 0.6 mmol) was then converted to the corresponding acid upon treatment with NaOH (1.1 eq, 27 mg), in MeOH:H₂O (1:1) (15 mL), for 4 hours at room temperature. EtOAc was added as well as water. The aqueous layer was collected and acidified with 1N HCl to pH 2.5, and reextracted with EtOAc. The organic layer was

dried over MgSO_4 . Upon filtration and evaporation of the solvents under reduced pressure, a foam was isolated in quantitative yields.

NMR data was as follows:

^1H NMR (300 MHz, CDCl_3): δ = 7.71 (bd, 2H), 7.34 (m, 7H), 7.20 (m, 1H), 7.01 (m, 2H), 6.80 (d, 2H, J = 8.37 Hz), 5.27 (m, 1H), 4.75 (m, 1H), 4.04 (m, 1H), 3.23-2.93 (m, 4H), 2.42 (s, 3H), 1.85 (m, 1H), 1.60 (d, 3H, J = 6.09 Hz), 1.36-1.26 (m, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ = 174.74, 172.22, 157.53, 145.00, 143.77, 133.42, 130.76, 130.58, 129.14, 128.60, 128.48, 127.94, 126.15, 116.57, 76.39, 62.73, 53.90, 50.09, 37.09, 25.07, 24.52, 22.17.

Mass Spectroscopy: (FAB) 537 (M+H).

Example 2

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-L-tyrosine

N-toluene-4-sulfonyl-L-proline (1.56 g, 6.93 mmol) was dissolved in 50 mL of DMF, with L-tyrosine methyl ester (1.1 eq, 1.76g), Et_3N (2.2 eq, 2.0 mL), and BOP reagent (1.1 eq, 3.36 g). The ester was isolated in 75% yield (2.14 g, 5.16 mmol). The ester (120 mg, 0.27 mmol) was taken up in a 1:1 mixture of MeOH: H_2O (5 mL) with 1.1 eq. of NaOH. The title acid was isolated in quantitative yield as an oil.

NMR data was as follows:

^1H NMR (300 MHz, CD_3OD): δ = 7.46 (d, 2H, J = 8.25 Hz), 7.12 (d, 2H, J = 7.83 Hz), 6.77 (d, 2H, J = 8.35 Hz), 6.49 (d, 2H, J = 8.39 Hz), 4.46 (m, 1H), 3.80 (m, 1H), 3.11-2.70 (m, 4H), 2.19 (s, 3H), 1.66 (m, 1H), 1.31 (m, 3H).

^{13}C NMR (75 MHz, CD_3OD): δ = 177.36, 176.12, 160.30, 149.12, 137.29, 134.79, 134.50, 132.22, 131.50, 119.63, 66.67, 57.90, 54.02, 41.06, 34.57, 28.54, 25.79.

Mass Spectroscopy: (FAB) 417 (M+H).

Example 3

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-4-carboxyphenylalanine

Diethyl 2-acetamidomalonate was treated with 4-cyanobenzyl
5 bromide and NaOEt in EtOH, to give after dilution with H₂O, and isolation
of the resulting precipitate, diethyl 2-acetamido-2-(4-cyanobenzyl)malonate.
This product was heated in HCl, and the mixture evaporated to give 4-
carboxy-D,L-phenylalanine hydrochloride [D,L-Phe(4-CO₂H)-OH·HCl].
This product was treated with MeOH and HCl gas to give after evaporation,
10 D,L-Phe(4-CO₂Me)-OMe·HCl. This product was treated with *N*-(toluene-4-
sulfonyl)-L-Pro-OH, BOP, and NMM in DMF, to give after aqueous workup
and flash chromatography, *N*-(toluene-4-sulfonyl)-L-Pro-D,L-Phe(4-
CO₂Me)-OMe. This product was treated with NaOH in dioxane and water,
to give after acidification, extraction, drying with MgSO₄, filtration and
15 evaporation the title compound as a clear oil.

NMR data was as follows:

¹H NMR (CD₃OD, 300 MHz): δ = 7.86 (d, *J* = 8.2, 1H), 7.83 (d, *J* =
8.2, 1H), 7.74 (d, *J* = 8.3, 1H), 7.73 (d, *J* = 8.3, 1H), 7.41 (d, *J* = 8.2, 2H),
7.31 (d, *J* = 8.2, 1H), 7.21 (d, *J* = 8.1, 1H), 4.53 (dd, *J* = 7.1, *J* = 4.7, 0.5H),
20 4.46 (dd, *J* = 5.9, 0.5H), 4.07-3.99 (m, 1H), 3.58-3.45 (m, 1H), 3.28-3.02 (m,
3H), 2.43 (s, 3H), 1.83-1.43 (m, 4H).

¹³C NMR (CD₃OD w/ CD₃ONa, 75 MHz): δ = 179.12, 179.08,
177.5, 177.4, 173.1, 173.0, 145.83, 145.80, 139.6, 139.4, 137.8, 137.7,
134.77, 134.75, 131.0, 130.9, 130.5, 130.4, 129.44, 129.39, 129.1, 129.0,
25 63.61, 63.57, 57.0, 56.9, 50.74, 50.70, 38.7, 38.6, 31.71, 31.65, 25.2, 25.1,
21.50, 21.49.

Mass Spectroscopy: (+FAB, 3-nitrobenzyl alcohol) 461 (M+H).

Example 4

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-3-(carboxy)phenylalanine

Substitution of 3-cyanobenzyl bromide for 4-cyanobenzyl bromide,
5 and following the methods for preparation of Example 3, gave the title
compound as a clear oil.

NMR data was as follows:

¹H NMR (CD₃OD, 300 MHz): δ = 7.82 (s, 0.5H), 7.77 (s, 0.5H), 7.73
(d, J = 8.2, 1H), 7.72 (d, J = 8.2, 1H), 7.40 (d, J = 8.2, 2H), 7.37-7.19 (m,
10 3H), 4.53 (dd, J = 7.5, J = 4.9, 0.5H), 4.46 (t, J = 5.9, 0.5H), 4.05 (dd, J = 8.2,
 J = 3.5, 0.5H), 3.99 (dd, J = 8.8, J = 3.4, 0.5H), 3.48-3.42 (m, 0.5H), 3.36-
2.99 (m, 3.5H), 2.42 (s, 3H), 1.88-1.38 (m, 4H).

¹³C NMR (CD₃OD w/ CD₃ONa, 75 MHz): δ = 179.18, 179.16,
177.6, 177.5, 173.04, 172.97, 145.82, 145.81, 139.5, 139.4, 137.81, 137.78,
15 134.77, 134.75, 132.33, 132.31, 131.03, 130.96, 130.7, 130.6, 129.87,
129.85, 129.4, 129.34, 128.96, 128.4, 63.6, 63.5, 57.0, 56.8, 50.77, 50.76,
38.72, 38.68, 31.7, 31.6, 25.4, 25.1, 21.50, 21.48.

Mass Spectroscopy: (+FAB, 3-nitrobenzyl alcohol) 461 (M+H).

20

Example 5

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-4-(2-carboxyphenoxy)-L-phenylalanine

N-(Toluene-4-sulfonyl)-L-prolyl-L-tyrosine methyl ester (2.14 g,
5.16 mmol) was added to a suspension of sodium hydride, 60% in oil (1.1
25 eq., 228 mg) in xylenes (50 mL) at 0°C. The reaction mixture was stirred for
5 minutes and cuprous bromide:dimethyl sulfide complex (1.4 eq., 1.48 g)
was added. The reaction mixture was stirred at 23°C for 0.5 hr. To this was
added sodium 2-iodobenzoate (1.5 eq., 8.06 mmol), and the reaction mixture
was refluxed for 12 hours. EtOAc (100 mL) was added, and the organic
30 layer washed with NH₄Cl, 10% HCl, and brine, then dried over MgSO₄. The

crude material was eluted on column chromatography (silica gel), with CHCl_3 :MeOH (9:1), and isolated as an oil. The acid was prepared by treatment with NaOH (1.1 eq), in MeOH:H₂O (1:1) for 4 hours at room temperature. The diacid was isolated as a foam.

5 NMR data was as follows:

¹H NMR (300 MHz, CDCl₃): δ = 7.71 (m, 2H), 7.29 (m, 4H), 7.19 (m, 4H), 6.72 (m, 1H), 4.84 (m, 1H), 4.13 (m, 1H), 3.39 (m, 1H), 3.11 (m, 3H), 2.43 (s, 3H), 1.89 (m, 1H), 1.48 (m, 3H).

10 ¹³C NMR (75 MHz, CDCl₃): δ = 172.67, 157.84, 155.89, 155.04, 145.17, 133.61, 133.19, 133.08, 131.69, 131.02, 130.64, 128.42, 127.87, 124.24, 120.04, 119.61, 116.12, 62.81, 50.31, 37.28, 30.69, 24.81, 22.15.

Mass Spectroscopy: (FAB) 553 (M+H).

Example 6

15

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-O-(benzyl)-L-tyrosine

N-(Toluene-4-sulfonyl)-L-Pro-OH was treated with (COCl)₂ and DMF in CH₂Cl₂ to give, after evaporation, *N*-(Toluene-4-sulfonyl)-L-Pro-Cl. This product was treated with L-Tyr(Bn)-OH and NaOH in THF and H₂O, to
20 give, after acidification, extraction, drying with MgSO₄, and evaporation the title compound as a clear oil.

NMR data was as follows:

25 ¹H NMR (DMSO-*d*₆, 300 MHz): δ = 8.04 (d, *J* = 8.2, 1H), 7.70 (d, *J* = 8.1, 2H), 7.42-7.21 (m, 6H), 7.15 (d, *J* = 8.5, 2H), 6.90 (d, *J* = 8.5, 2H), 5.04 (s, 2H), 4.49-4.42 (m, 1H), 4.13-4.09 (m, 1H), 3.33-3.27 (m, 2H), 3.10-2.89 (m, 3H), 2.38 (s, 3H), 1.60-1.35 (m, 4H).

¹³C NMR (DMSO-*d*₆, 75 MHz): δ = 172.63, 170.8, 157.0, 143.6, 137.2, 133.8, 130.3, 129.8, 129.4, 128.9, 128.4, 127.6, 125.3, 114.4, 69.1, 61.3, 53.4, 49.0, 35.8, 30.4, 23.8, 21.0.

30

Mass Spectroscopy: (+FAB, 3-nitrobenzyl alcohol) 523 (M+H).

Example 7

**Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-4-(iodo)-L-phenylalanine**

Following the experimental procedure described for the synthesis of
5 Example 8, affords the title compound as a foam.

NMR data was as follows:

¹H NMR (300 MHz, DMSO-d₆): δ = 8.30 (d, 1H, *J* = 8.40 Hz), 7.87
(d, 2H, *J* = 8.50 Hz), 7.78 (d, 2H, *J* = 8.50 Hz), 7.55 (d, 2H, *J* = 8.30 Hz),
7.25 (d, 2H, *J* = 8.30 Hz), 4.63 (m, 1H), 4.26 (m, 1H), 3.20 (m, 4H), 2.53 (s,
10 3H), 1.75 (m, 4H).

Mass Spectroscopy: (FAB) 543 (M+H).

Example 8

**Synthesis of
15 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(methoxy)-phenylalanine**

Following the experimental procedure described for Example 1, *N*-
(toluene-4-sulfonyl)-L-proline (861 mg, 3.2 mmol) was dissolved in 20 mL
of DMF, with Et₃N (2.0 eq, 981 μL), BOP (1.1 eq, 1.55 g), and O-methyl-L-
tyrosine methyl esterHCl salt (1.1 eq). The methyl ester was isolated in 25%
20 yield (370 mg, 0.80 mmol). It was then hydrolyzed in a 1:1 solution of
MeOH: H₂O (5 mL), with NaOH (1.1 eq, 35 mg). The acid was isolated as a
foam, in 60% yield (216 mg, 0.48 mmol).

NMR data was as follows:

¹H NMR (300 MHz, CDCl₃): δ = 7.72 (d, 2H, *J* = 7.80 Hz), 7.46 (d,
25 1H, *J* = 6.30 Hz), 7.33 (d, 2H, *J* = 7.20 Hz), 7.26 (d, 2H, *J* = 7.80 Hz), 7.14
(d, 2H, *J* = 8.40 Hz), 5.65 (bs, 2H), 4.82 (m, 1H), 4.10 (m, 1H), 3.75 (s, 3H),
3.35-3.01 (m, 4H), 2.42 (s, 3H), 1.97 (m, 1H), 1.48 (m, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ = 174.57, 172.25, 159.18, 145.07, 133.40, 130.97, 130.59, 128.66, 128.44, 114.53, 62.78, 55.84, 54.09, 50.20, 37.09, 30.48, 24.68, 22.15.

Mass Spectroscopy: (FAB) 447 (M+H).

5

Example 9

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-4-nitro-L-phenylalanine

N-(toluene-4-sulfonyl)-L-proline (955 mg, 3.4 mmol) was dissolved
10 in dry DMF (50 mL) with L-(4-nitro)-phenylalanine methyl ester (1.1 eq, 777 mg), Et_3N (2.2 eq, 1.04 mL), and BOP reagent (1.1 eq, 1.65 g). The desired methyl ester was isolated in 40% yield (500 mg, 1.05 mmol). The ester was hydrolyzed in a 1:1 solution of MeOH: H_2O (10 mL) with NaOH (1.1 eq, 42 mg). The title compound was isolated as an oil in 51% yield (246
15 mg, 0.53 mmol).

NMR data was as follows:

^1H NMR (300 MHz, CDCl_3): δ = 8.10 (d, 2H, J = 8.79 Hz), 7.81 (d, 1H, J = 8.25 Hz), 7.68 (d, 2H, J = 8.22 Hz), 7.42 (d, 2H, J = 8.79 Hz), 7.32 (d, 2H, J = 8.25 Hz), 4.93 (m, 1H), 4.09 (m, 1H), 3.44 (m, 2H), 3.24 (m, 1H),
20 3.04 (m, 1H), 2.38 (s, 3H), 1.83 (m, 1H), 1.38 (m, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ = 174.25, 173.00, 147.87, 145.34, 145.06, 133.06, 131.13, 130.73, 128.42, 124.18, 62.62, 53.29, 50.04, 37.48, 30.21, 24.35, 21.76.

Mass Spectroscopy: (FAB) 462 (M+H).

25

Example 10

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-4-(*O*-*tert*-butyl)-L-tyrosine

Following the experimental procedure described in Example 8, the
30 desired material was isolated as a solid, mp = dec $>80^\circ\text{C}$.

NMR data was as follows:

¹H NMR (300 MHz, CDCl₃): δ = 7.66 (d, 2H, *J* = 8.40 Hz), 7.32 (d, 2H, *J* = 8.01 Hz), 7.09 (d, 2H, *J* = 8.37 Hz), 6.91 (d, 2H, *J* = 7.86 Hz), 4.75 (m, 1H), 4.00 (m, 1H), 3.25 (m, 2H), 3.05 (m, 2H), 2.40 (s, 3H), 1.95 (m, 4H), 1.27 (s, 9H).

Mass Spectroscopy: (FAB) 489 (M+H).

Example 11

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-L-(3,5-diiodo)-tyrosine

Following the experimental procedure described in Example 8 but substituting 3,5-diiodo-L-tyrosine methyl ester HCl salt for the O-methyl-L-tyrosine provided for the title compound as a foam.

NMR data was as follows:

¹H NMR (300 MHz, CDCl₃): δ = 7.74 (d, 2H, *J* = 8.19 Hz), 7.51 (s, 1H), 7.42 (m, 1H), 7.36 (d, 2H, *J* = 8.22 Hz), 7.26 (s, 1H), 4.75 (m, 1H), 4.12 (m, 1H), 3.55 (m, 1H), 3.24 (m, 2H), 3.05 (m, 1H), 2.44 (s, 3H), 1.62 (m, 4H).

Mass Spectroscopy: (FAB) 685 (M+H), 713 (M+Na).

Example 12

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-L-4-(aminobenzoyl)-phenylalanine

Following the experimental procedure described for Example 1, the title compound was isolated as an oil in quantitative yields.

NMR data was as follows:

¹H NMR (300 MHz, CD₃OD): δ = 7.70 (d, 2H, *J* = 8.50 Hz), 7.62 (d, 2H, *J* = 8.50 Hz), 7.44-7.17 (m, 5H), 7.20 (d, 2H, *J* = 8.25 Hz), 7.06 (d, 2H, *J* = 8.52 Hz), 4.47 (m, 1H), 3.89 (m, 1H), 3.18 (m, 1H), 3.05-2.83 (m, 3H), 2.20 (s, 3H), 1.60-1.39 (m, 4H).

¹³C NMR (75 MHz, CD₃OD): δ = 177.08, 171.91, 148.83, 141.80, 139.37, 138.10, 137.48, 136.92, 134.12, 132.72, 132.37, 131.69, 125.32, 66.34, 58.09, 53.70, 40.85, 34.78, 28.47, 24.61.

Mass Spectroscopy: (FAB) 537 (M+H).

5

Preparative Example A

Synthesis of *N*-(Toluene-4-sulfonyl)-D-prolyl-D-phenylalanine

Boc-D-Pro-OH and D-Phe-OBn·HCl were treated with BOP and
10 NMM in DMF, to give after aqueous workup and flash chromatography,
Boc-D-Pro-D-Phe-OBn. This product was treated with TFA and anisole, and
the mixture was evaporated. The residue was dissolved in Et₂O and washed
with saturated aqueous NaHCO₃ and saturated aqueous NaCl. The Et₂O
layers were dried with MgSO₄, filtered, and evaporated to give D-Pro-D-Phe-
15 OBn. This product was treated with CH₃SO₂Cl and Et₃N in CH₂Cl₂, to give
after aqueous workup and flash chromatography, *N*-(CH₃SO₂)-D-Pro-D-Phe-
OBn. This product was treated with 10% Pd on C in THF, and the mixture
was shaken under 50 psi H₂. The mixture was filtered through Celite, and
evaporated to give the title compound as a solid, mp = 71-75°C.

20 NMR data was as follows:

¹H NMR (CDCl₃, 300 MHz): δ = 1.24-1.54 (m, 3H), 1.95 (m, 1H),
2.43 (s, 3H), 3.10 (m, 2H), 3.32 (m, 2H), 4.09 (m, 1H), 4.82 (m, 1H), 7.10-
7.40 (m, 7H), 7.69 (d, 2H, *J* = 8.0 Hz).

¹³C NMR (CDCl₃, 75 MHz): δ = 22.1, 25.8, 32.2, 38.8, 55.4, 63.8,
25 128.5, 129.5, 130.0, 131.1, 131.6, 135.5, 138.7, 146.3, 174.58, 174.63.

Mass Spectroscopy: (FAB+) 417 (M+H).

Example 13

**Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-L-(3-iodo-4-hydroxy)-phenylalanine**

The title compound was prepared according to the procedure described for the synthesis described in Example 8. The corresponding material was isolated as a film.

NMR data was as follows:

¹H NMR (300 MHz, DMSO-d₆): δ = 7.72 (d, 2H, *J* = 8.50 Hz), 7.42 (s, 1H), 7.43 (d, 2H, *J* = 8.50 Hz), 7.08 (d, 1H, *J* = 8.05 Hz), 6.75 (d, 1H, *J* = 8.05 Hz), 4.81 (m, 1H), 4.11 (m, 1H), 3.45 (m, 1H), 3.20 (m, 2H), 2.98 (m, 1H), 2.62 (m, 1H), 2.44 (s, 3H), 1.96 (m, 2H).

Example 14

**Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-L-(4-chloro)phenylalanine**

The title compound was prepared from the product of Example 37 using the procedure described in Method 7, mp = >200°C

Example 15

**Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-L-leucine**

N-(Toluene-4-sulfonyl)-L-proline hydrate was coupled to L-leucine methyl ester hydrochloride using the procedure described in Method 3. The title compound was prepared via hydrolysis of the methyl ester using LiOH in THF/water.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 9.80 (bs, 1H), 7.72 (d, 2H, *J* = 8.0 Hz), 7.47 (d, 1H, *J* = 8.0 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 4.56 (m, 1H), 4.16 (m, 1H), 3.51 (m, 1H), 3.17 (m, 1H), 2.38 (s, 3H), 2.12 (m, 1H), 1.73-1.54 (6H), 0.91 (d, 3H, *J* = 6.5 Hz), 0.89 (d, 3H, *J* = 6.0 Hz).

^{13}C NMR (CDCl_3): $\delta = 176.2, 172.5, 145.0, 133.4, 130.6, 128.4, 62.7, 51.7, 50.3, 41.4, 30.5, 25.5, 23.4, 22.4, 22.1$.

Mass Spectroscopy: FAB m/e 383 ($\text{M}+\text{H}$).

5

Example 16

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-L-alanine

N-(Toluene-4-sulfonyl)-L-proline hydrate was coupled to L-alanine methyl ester hydrochloride using the procedure described in Method 3. The resulting methyl ester was deesterified via hydrolysis using LiOH in THF/water to provide the title compound as a solid, $\text{mp} = 160.5\text{-}162.5^\circ\text{C}$.

10

NMR data was as follows:

^1H NMR (CDCl_3): $\delta = 7.76$ (d, 2H, $J = 8.2$ Hz), 7.52 (d, 1H, $J = 6.7$ Hz), 7.37 (d, 2H, $J = 8.0$ Hz), 4.56 (p, 1H, $J = 7.1$ Hz), 4.14 (dd, 1H, $J = 2.6, 8.5$ Hz), 3.56 (m, 1H), 3.21 (dt, 1H, $J = 6.6, 9.7$ Hz), 2.45 (s, 3H), 2.21 (m, 1H), 1.78 (m, 1H), 1.62 (m, 2H), 1.52 (d, 3H, $J = 7.1$ Hz).

15

^{13}C NMR (CDCl_3): $\delta = 176.4, 172.3, 145.1, 133.3, 130.6, 128.5, 62.7, 50.4, 49.1, 30.5, 25.0, 22.2, 18.5$.

Mass Spectroscopy: FAB m/e 341 ($\text{M}+\text{H}$).

20

Example 17

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-L-4-(acetamido)-phenylalanine

The title compound was prepared from the product of Example 39 using the procedure described in Method 6.

25

NMR data was as follows:

^1H NMR (300 MHz, CD_3OD): $\delta = 7.50$ (d, 2H, $J = 8.25$ Hz), 7.28 (d, 2H, $J = 8.37$ Hz), 7.17 (d, 2H, $J = 8.20$ Hz), 6.99 (d, 2H, $J = 8.37$ Hz), 4.50 (m, 1H), 3.92 (m, 1H), 3.17 (m, 1H), 3.04 (m, 2H), 2.81 (m, 1H), 2.19 (s, 3H), 1.87 (s, 3H), 1.56 (m, 1H), 1.40 (m, 3H).

30

^{13}C NMR (75 MHz, CD_3OD): δ = 174.61, 172.14, 146.30, 139.29, 135.47, 134.38, 131.64, 131.48, 129.54, 121.71, 63.82, 55.36, 51.20, 38.27, 32.26, 25.93, 24.50, 22.19.

Mass Spectroscopy: (FAB) 474 (M+H).

5

Example 18

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-L-isoleucine

N-(Toluene-4-sulfonyl)-L-proline hydrate was coupled to L-isoleucine methyl ester hydrochloride using the procedure described in Method 3. The title compound was prepared via hydrolysis of the methyl ester using LiOH in THF/water.

NMR data was as follows:

^1H NMR (CDCl_3): δ = 7.72 (d, 2H, J = 8.3 Hz), 7.46 (d, 1H, J = 7.5 Hz), 7.36 (d, 2H, J = 8.1 Hz), 4.54 (dt, 1H, J = 5.4, 7.6 Hz), 4.16 (dd, 1H, J = 2.6, 8.7 Hz), 3.54 (m, 1H), 3.21 (m, 1H), 2.44 (s, 3H), 2.20 (m, 1H), 1.97 (m, 1H), 1.33-1.57 (4H), 1.35 (m, 4H), 0.90 (d, 3H, J = 7.0 Hz).

^{13}C NMR (CDCl_3): δ = 176.2, 172.2, 145.1, 133.4, 130.6, 128.5, 62.8, 53.3, 50.4, 32.1, 30.4, 28.0, 25.1, 22.8, 22.2, 14.5.

Mass Spectroscopy: FAB m/e 383 (M+H).

20

Example 19

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-L-aspartic acid

N-(Toluene-4-sulfonyl)-L-proline hydrate was coupled to L-4-(1,1-dimethylethyl)-aspartic acid methyl ester hydrochloride using the procedure described in Method 3. The methyl ester was hydrolyzed using LiOH in THF/water to provide a solid, mp = 153-155°C. The title compound was prepared, via cleavage of the *t*-butyl ester using trifluoroacetic acid in CH_2Cl_2 , as a solid, mp = 174-176°C.

30

NMR data was as follows:

¹H NMR (DMSO-d₆): δ = 8.27 (d, 1H, J = 8.0 Hz), 7.75 (d, 2H, J = 8.2 Hz), 7.44 (d, 2H, J = 8.2 Hz), 4.54 (m, 1H), 4.16 (m, 1H), 3.38 (m, 1H), 3.13 (m, 1H), 2.74 (dd, 1H, J = 5.9, 16.7 Hz), 2.63 (dd, 1H, J = 6.3, 16.7 Hz),
5 2.41 (s, 3H), 1.75 (m, 2H), 1.51 (m, 2H).

¹³C NMR (DMSO-d₆): δ = 172.5, 172.2, 171.3, 144.0, 134.3, 130.2, 127.9, 61.7, 49.3, 48.9, 36.2, 30.9, 24.3, 21.4.

Mass Spectroscopy: FAB m/e 385 (M+H).

10

Example 20

Synthesis of *N*-(Toluene-4-sulfonyl)-L-prolyl-L-lysine

N-(Toluene-4-sulfonyl)-L-proline hydrate was coupled to L-ε-Cbz-lysine methyl ester hydrochloride using the procedure described in Method 3.

15

The methyl ester was hydrolyzed using LiOH in THF/water. The title compound was prepared using the procedure described in Method 4 as a solid, mp = >200°C.

Example 21

20

Synthesis of *N*-(Toluene-4-sulfonyl)-L-prolyl-L-glutamic acid

N-(Toluene-4-sulfonyl)-L-proline hydrate was coupled to L-5-(1,1-dimethylethyl)-glutamic acid methyl ester hydrochloride using the procedure described in Method 3. The methyl ester was hydrolyzed using LiOH in

25

THF/water to provide a solid, mp = 164-166°C. The title compound was prepared, via cleavage of the t-butyl ester using trifluoroacetic acid in CH₂Cl₂, as a solid, mp = >200°C.

Example 22

Synthesis of
***N*-(Toluene-4-sulfonyl)-L-prolyl-L-**
(4-dibenzylamino)-phenylalanine methyl ester

5 The title compound was prepared using the procedure described in Method 9. The crude product was purified by flash chromatography (silica, 1:1 EtOAc:hexane) to afford the methyl ester as a white solid, mp = 60-65°C.

Example 23

Synthesis of
***N*-(Toluene-4-sulfonyl)-L-prolyl-L-(*N*-benzyl)-histidine**

10 *N*-(Toluene-4-sulfonyl)-L-proline hydrate was coupled to L-(*N*-benzyl)-histidine methyl ester dihydrochloride using the procedure described in Method 3. The title compound was prepared via hydrolysis of the methyl ester using LiOH in THF/water.

NMR data was as follows:

15 ¹H NMR (DMSO-d₆): δ = 8.15 (2, 1H, *J* = 7.8 Hz), 7.72 (m, 3H), 7.42 (d, 2H, *J* = 8.0 Hz), 7.37-7.21 (6H), 6.96 (s, 1H), 5.11 (s, 2H), 4.42 (m, 1H), 4.09 (m, 1H), 3.29 (m, 1H), 3.04 (m, 1H), 2.90 (m, 3H), 2.40 (s, 3H), 1.65-1.39 (4H).

20 ¹³C NMR (DMSO-d₆): δ = 173.1, 171.0, 144.0, 138.0, 137.7, 137.1, 134.2, 130.2, 129.0, 128.9, 128.0, 127.9, 117.3, 61.8, 52.5, 49.9, 49.3, 30.7, 30.1, 24.1, 21.4.

25 Mass Spectroscopy: FAB *m/e* 497 (M+H).

Example 24

Synthesis of
***N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-dibenzylamino)-phenylalanine**

30 The methyl ester was prepared using the procedure described in Example 22. The crude product was purified by flash chromatography

(silica, 1:1 EtOAc:hexane) to afford the methyl ester as a white solid, mp = 60-65°C. The title compound was then prepared using the procedure described in Method 5.

NMR data was as follows:

5 ¹H NMR (DMSO-d₆, 400 MHz): δ = 7.72 (d, 2H, J = 8.34Hz); 7.55 (d, 1H, J = 5.71Hz); 7.4 (d, 2H, J = 7.9Hz); 7.24 (m, 4H); 7.18 (m, 6H); 6.76 (d, 2H, J = 8.56Hz); 6.44 (d, 2H, J = 8.56Hz); 4.58 (d, 4H, J = 3.07Hz); 3.89 (dd, 1H, J = 2.74, 8.89Hz); 3.76 (m, 1H); 2.92 (m, 4H); 2.39 (s, 3H); 1.61 (m, 1H); 1.05-1.34 (m, 3H).

10 IR (KBr, cm⁻¹) 3400, 1655, 1620, 1520, 1405, 1300, 1160.

Mass Spectroscopy: ((+) FAB, m/e (%)) 634 (20 [M+ Li]⁺); 612 (100 [M+H]⁺).

Example 25

15 **Synthesis of N-(Toluene-4-sulfonyl)-L-prolyl-L-methionine**

N-(Toluene-4-sulfonyl)-L-proline hydrate was coupled to methionine methyl ester using the procedure described in Method 3. The title compound was prepared via hydrolysis of the methyl ester using LiOH in THF/water.

20 NMR data was as follows:

¹H NMR (CDCl₃): δ = 9.05 (bs, 1H), 7.76 (d, 2H, J = 8.2 Hz), 7.69 (d, 1H, J = 7.7 Hz), 7.37 (d, 2H, J = 7.9 Hz), 4.68 (m, 1H), 4.16 (m, 1H), 3.57 (m, 1H), 3.20 (m, 1H), 2.59 (t, 2H, J = 7.4 Hz), 2.45 (s, 1H), 2.21 (m, 3H), 2.19 (s, 3H), 1.79 (m, 1H), 1.63 (m, 2H).

25 ¹³C NMR (CDCl₃): δ = 174.5, 172.0, 144.5, 132.6, 130.0, 127.9, 62.2, 51.9, 49.8, 30.8, 30.0, 29.9, 24.5, 21.6, 15.4.

Mass Spectroscopy: FAB m/e 401 (M+H).

Example 26

**Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-L-serine**

The title compound was prepared via hydrogenolysis of the
5 corresponding benzyl ether using 10% Pd/C in EtOH/HOAc (20:1). The
reaction mixture was filtered through celite and the filtrate was evaporated in
vacuo to give a residue which was lyophilized from water to give the title
compound as a white solid.

NMR data was as follows:

10 ^1H NMR (CDCl_3): δ = 7.97 (d, 1H, J = 7.1 Hz), 7.74 (d, 2H, J = 8.0
Hz), 7.33 (d, 2H, J = 8.4 Hz), 4.62 (m 1H), 4.21-3.94 (2H), 3.60 (m, 1H),
3.17 (m, 1H), 2.41 (s, 3H), 2.07 (m, 1H), 1.88-1.55 (3H).

^{13}C NMR (CDCl_3): δ = 172.8, 144.4, 132.8, 130.0, 127.8, 62.3, 55.0,
49.8, 30.8, 30.2, 24.4, 21.5.

15 Mass Spectroscopy: FAB m/e 357 ($\text{M}+\text{H}$).

Preparative Example B

**Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-D-aspartic acid**

20 *N*-Benzyloxycarbonyl-D-4-(1,1-dimethylethyl)-aspartic acid was con-
verted to the methyl ester using the procedure described in Method 2. D-4-
(1,1-dimethylethyl)-aspartic acid methyl ester was prepared from the product
of the previous step utilizing the procedure described in Method 4. *N*-
(Toluene-4-sulfonyl)-L-proline hydrate was coupled to the resulting D-4-
25 (1,1-dimethylethyl)-aspartic acid methyl ester utilizing the procedure
described in Method 3. The methyl ester was hydrolyzed using the
procedure described in Method 6. The product was isolated as a white solid,
mp = 55°C. The title compound was then prepared using the procedure
described in Method 11. The product was isolated as a white solid, mp =
30 131-132°C.

NMR data was as follows:

¹H NMR (DMSO-d₆, 300 MHz): δ = 8.19 (d, 1H, *J* = 8.0 Hz); 7.73 (d, 2H, *J* = 7.0 Hz); 7.43 (d, 2H, *J* = 8.0 Hz); 4.55, (m, 1H); 4.12, (m, 1H); 3.40 (m, 1H); 3.13 (m, 1H); 2.60 (m, 2H); 2.41 (s, 3H); 1.76 (m, 2H); 1.55 (m, 2H).

¹³C NMR (DMSO-d₆, 75 MHz): δ = 172.5, 172.2, 171.3, 144.0, 134.2, 130.2, 127.9, 61.8, 49.4, 48.8, 36.2, 30.9, 24.2, 21.4.

Mass Spectroscopy: (PI-FAB) 385, (M+H)⁺.

10

Preparative Example C

Synthesis of *N*-(Toluene-4-sulfonyl)-L-prolyl-D-glutamic acid

N-Benzyloxycarbonyl-D-5-(1,1-dimethylethyl)-glutamic acid was converted to the methyl ester using the procedure described in Method 2. D-5-(1,1-dimethylethyl)-glutamic acid methyl ester was prepared from the product of the previous step utilizing the procedure described in Method 4. *N*-(Toluene-4-sulfonyl)-L-proline hydrate was coupled to the resulting D-5-(1,1-dimethylethyl)-glutamic acid methyl ester utilizing the procedure described in Method 3. The methyl ester was hydrolyzed using the procedure described in Method 6. The product was isolated as a white solid, mp = 50°C.

The title compound was then prepared using the procedure described in Method 11. The product was isolated as a white solid, mp = 60°C.

NMR data was as follows:

¹H NMR (DMSO-d₆, 300 MHz): δ = 8.12 (d, 1H, *J* = 4.0 Hz); 7.73 (m, 2H); 7.43, (m, 2H); 4.25 (m, 1H); 4.05 (m, 1H); 3.43 (m, 1H); 3.15 (m, 1H); 2.40 (s, 3H), 2.45 (m, 2H); 2.02 (m, 2H); 1.90 - 1.40 (bm, 4H).

¹³C NMR (DMSO-d₆, 75 MHz): δ = 174.3, 173.3, 171.6, 144.0, 134.1, 130.3, 127.8, 61.9, 51.4, 49.5, 31.2, 30.3, 26.3, 24.3, 21.4.

30

Mass Spectroscopy: (PI-FAB) 399, (M+H)⁺.

Example 27

**Synthesis of
N-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)
thiaprolyl-L-(N-benzyl)-histidine**

5 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiazolidine-4-carboxylic acid was prepared from L-(5,5-dimethyl)-thiazolidine-4-carboxylic acid using the procedure described in Method 1. The title compound was then prepared using standard coupling procedures to provide a solid, mp = >200°C (dec.).

10 NMR data was as follows:

¹H NMR (D₂O, 300 MHz): δ = 0.95 (s, 3H), 1.08 (s, 3H), 2.41 (s, 3H), 2.85-3.12 (m, 2H), 3.84 (s, 1H), 4.32 (m, 1H), 4.40 (s, 2H), 5.09 (s, 2H), 7.01 (s, 1H), 7.24-7.43 (m, 7H), 7.60-7.71 (m, 3H).

15 ¹³C NMR (D₂O, 75 MHz): δ = 27.9, 30.2, 30.3, 35.6, 37.0, 57.7, 61.3, 61.7, 79.8, 124.9, 134.6, 135.06, 135.10, 135.8, 137.1, 138.9, 143.2, 143.4, 143.5, 152.6, 176.7, 184.1.

Mass Spectroscopy: (FAB+) 565 (M+H).

Example 28

20 **Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-L-(1-methyl)histidine**

The ester of the title compound was synthesized as described in Method 12. The ester was dissolved in dioxane/H₂O (8 mL) to which was added solid NaOH (1 eq.). After stirring overnight, the reaction mixture was concentrated. The residue was redissolved in H₂O and loaded onto an ion exchange column (Dowex 50W-X8-100, H⁺ form). After washing the column with H₂O, the compound was eluted with 5% aqueous pyridine. Fractions containing the compound were pooled and concentrated and the residue was dissolved in H₂O and lyophilized. The product was isolated as a white solid, mp = 135-137°C.

25

30

NMR data was as follows:

¹H NMR(DMSO-d₆, 300 MHz): δ = 8.16 (d, 2H, J = 8.0 Hz); 7.72 (d, 2H, J = 8.0 Hz); 7.54 (s, 1H); 7.42 (d, 2H, J = 8.0 Hz); 6.91 (s, 1H); 5.10 (bs, 1 H); 4.41 (m, 1H); 4.11 (M, 1H); 3.57 (s, 3H), 3.34 (m, 1H); 3.10 (m, 1H); 2.92 (m, 2 H); 2.39 (s, 3 H); 1.80-1.45 (bm, 4H).

5 ¹³C NMR(DMSO-d₆, 75 MHz): δ = 173.0, 171.0, 143.9, 137.5, 136.9, 134.3, 130.2, 127.8, 118.6, 61.8, 52.5, 49.3, 33.3, 30.8, 29.9, 24.2, 21.4.

Mass Spectroscopy: (PI-FAB) 421, (M+H)⁺.

Example 29

10

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-D-(*N*-benzyl)histidine

A CH₂Cl₂ solution of Boc-D-(*N*-benzyl)histidine was chilled to -15°C (dry ice/CH₃CN bath) to which was added diethylisopropylamine (1.5 eq.), methanol (3.0 eq.) and BOP (1.1 eq) to form the methyl ester. The
15 reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was then poured into 0.1 M HCl and the organic phase washed with H₂O, saturated NaHCO₃, brine, dried (MgSO₄), filtered and concentrated. The crude methyl ester was purified by column chromatography. The Boc group was removed with TFA/CH₂Cl₂. The crude
20 reaction mixture was taken-up in CH₂Cl₂ and washed with 5% Na₂CO₃. The organic phase was washed with brine and dried (MgSO₄), filtered and concentrated to give the free amine. The coupling was performed using the procedure described in Method 12 and the ester hydrolyzed using the procedure described in Method 7. The product was isolated as a white solid,
25 mp = >200°C.

NMR data was as follows:

¹H NMR (DMSO-d₆, 300 MHz): δ = 7.75 - 7.61 (m, 3 H); 7.51 (s, 1H); 7.45-7.15 (bm, 7 H); 6.89 (s, 1H); 5.05 (m, 2H); 4.05 (m, 2H); 3.30 (m, 1 H); 3.10 (m, 1H); 2.95 (m, 1H); 2.75 (m, 1H); 2.38 (s, 3H); 1.67 (m, 2H);
30 1.35 (m, 2H).

^{13}C NMR (DMSO- d_6 , 75 MHz): δ = 1740.3, 169.6, 143.9, 139.3, 138.3, 136.5, 134.1, 130.3, 128.9, 127.8, 127.7, 117.1, 62.4, 54.3, 49.8, 49.4, 31.8, 30.6, 24.2, 21.4.

Mass Spectroscopy: (PI-FAB) 519, (M+H) $^+$.

5

Example 30

Synthesis of *N*-(Toluene-4-sulfonyl)-L-glutamyl-L-tyrosine

Cbz-L-5-(1,1-dimethylethyl)-glutamic acid was coupled with L-tyrosine *t*-butyl ester using the procedure described in Method 3. The Cbz group was removed using the procedure described in Method 4. The resulting ester was tosylated using the procedure described in Method 1. The title compound was prepared using the procedure outlined in Method 11 which provided a solid, mp = 173-175°C.

15 NMR data was as follows:

^1H NMR (DMSO- d_6 , 300 MHz): δ = 1.70-1.90 (m, 2H), 2.24-2.32 (m, 2H), 2.40 (s, 3H), 2.80-3.10 (m, 2H), 3.51 (m, 1H), 4.0-4.5 (C-H buried under large H_2O peak), 6.87 (d, 2H, J = 8.4 Hz), 7.18 (d, 2H, J = 8.2 Hz), 7.44 (d, 2H, J = 8.2 Hz), 7.70 (d, 2H, J = 8.2 Hz), 8.34 (bs, 1H).

20 ^{13}C NMR (DMSO- d_6 , 75 MHz): δ = 21.5, 28.5, 31.1, 36.7, 52.9, 54.8, 121.9, 128.5, 130.6, 131.1, 131.9, 138.0, 146.1, 147.9, 170.7, 173.0, 174.7.

Mass Spectroscopy: (FAB+) 465 (M+H).

Example 31

25 Synthesis of *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(*N*-3-methyl)histidine

Boc-L-(3-methyl)histidine was dissolved in MeOH and chilled in an ice bath. HCl gas was then bubbled through the reaction mixture for 15 minutes. After stirring overnight, the reaction mixture was concentrated to a gummy solid. The dihydrochloride was coupled to Tos-Pro-OBn using the

30

procedure described in Method 12 and hydrolyzed via Method 7. The product was isolated as a white solid, mp = >200°C.

NMR data was as follows:

¹H NMR (DMSO-d₆, 300 MHz): δ = 7.74 (m, 3H); 7.45 - 7.35 (bm, 3H); 6.56 (s, 1H); 4.10-3.93 (m, 2H); 3.51 (s, 3 H), 3.22 (m, 1H), 3.10 (m, 2H); 2.91 (m, 1H); 2.38 (s, 3 H); 1.70 (m, 1H); 1.45 (m, 3H).

¹³C NMR (DMSO-d₆, 75 MHz): δ = 173.3, 170.1, 144.1, 137.5, 133.9, 130.3, 128.8, 128.1, 127.5, 62.4, 53.6, 49.1, 31.2, 30.6, 26.2, 24.1, 21.4.

Mass Spectroscopy: (PI-FAB) 443, (M+H)⁺.

Example 32

Synthesis of *N*-(Toluene-4-sulfonyl)-L-prolyl-α-amino-2,3-dihydro-(1,4-benzodioxin)-6-propanoic acid

The title compound was prepared using the procedure described in Method 16 and isolated as a white solid.

NMR data was as follows:

¹H NMR (CDCl₃, 300 MHz): δ = 7.73 (m, 2H); 7.32 (m, 2H); 6.87-6.26 (m, 2 H); 6.64 (m, 1H); 4.84 (m, 1 H); 4.21 (m, 4H), 4.10 (m, 1H); 3.55-3.40 (m, 1H); 3.30-2.95 (m, 3H); 2.43 (m, 3H); 2.06 (m, 1 H); 1.64 (m, 3H).

¹³C NMR (CDCl₃, 75 MHz): δ = 175.0, 174.5, 172.4, 172.3, 145.0, 144.9, 144.2, 143.9, 143.4, 143.2, 133.5, 133.4, 130.6, 129.6, 129.1, 128.5, 123.2, 122.69, 118.9, 118.7, 118.1, 117.9, 64.9, 63.1, 62.8, 53.9, 53.8, 50.4, 50.2, 37.3, 37.2, 30.9, 30.5, 24.8, 24.7, 22.2.

Mass Spectroscopy: (PI-FAB) 475, (M+H)⁺.

Example 33

**Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-
 α -amino-1,3-benzodioxole-5-propanoic acid**

5 The title compound was prepared using the procedure described in Method 16 and isolated as a white solid.

NMR data was as follows:

^1H NMR (CDCl_3 , 300 MHz): δ = 7.71 (m, 2H); 7.50 - 7.29 (bm, 3H);
7.81-7.60 (m, 3H); 5.90 (m, 2H); 4.80 (m, 1H); 4.15 (m, 1H); 3.43 (m, 1H);
10 3.30-3.00 (bm, 3H); 2.41 (s, 3H); 2.10 (m, 1H); 1.70 (m, 1H); 1.51 (m, 2H).

^{13}C NMR (CDCl_3 , 75 MHz): δ = 174.9, 174.5, 172.5, 172.3, 148.5,
148.2, 147.4, 147.2, 145.0, 133.4, 133.2, 130.6, 130.2, 129.5, 128.5, 128.5,
123.6, 123.1, 110.5, 110.2, 109.2, 108.8, 101.5, 63.1, 62.7, 54.0, 53.7, 50.4,
50.2, 37.8, 37.6, 31.0, 30.4, 24.8, 22.1.

15 Mass Spectroscopy: (PI-FAB) 461, (M+H) $^+$.

Example 34

**Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-L-valine**

20 N-(Toluene-4-sulfonyl)-L-proline hydrate was coupled to L-valine methyl ester hydrochloride using the procedure described in Method 3. The title compound was prepared via hydrolysis of the methyl ester using LiOH in THF/water.

NMR data was as follows:

25 ^1H NMR (CDCl_3): δ = 8.20 (br s, 1H), 7.76 (d, 2H, J = 8. Hz), 7.49 (d, 1H, J = 8.3 Hz), 7.35 (d, 2H, J = 8.0 Hz), 4.50 (dd, 1H, J = 4.8, 8.3 Hz), 4.19 (m, 3H), 3.54 (m, 1H), 3.21 (m, 1H), 2.44 (s, 3H), 2.31-2.18 (2H), 1.70-1.56 (3H), 1.00 (d, 3H, J = 6.9 Hz), 0.99 (d, 2H, J = 6.9 Hz).

^{13}C NMR (CDCl_3): δ = 175.7, 172.3, 145.0, 133.5, 130.6, 128.5, 62.8,
30 58.1, 50.3, 31.6, 30.3, 25.1, 22.2, 19.7, 18.2.

Mass Spectroscopy: FAB m/e 369 (M+H).

Example 35

**Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-L-(4-iodo)-phenylalanine methyl ester**

The procedure used for the preparation of Example 8 was utilized.

5 The title compound was isolated as a white foam.

NMR data was as follows:

¹H NMR (300 MHz, CDCl₃): δ = 7.72 (d, 2H, J = 8.25 Hz), 7.64 (d, 2H, J = 8.25 Hz), 7.41 (d, 1H, J = 8.20 Hz), 7.36 (d, 2H, J = 8.10 Hz), 7.00 (d, 2H, J = 8.25 Hz), 4.82 (m, 1H), 4.08 (m, 1H), 3.71 (s, 3H), 3.35 (m, 2H),
10 3.10 (m, 2H), 2.44 (s, 3H), 2.01 (m, 1H), 1.55 (m, 3H).

Mass Spectroscopy: (FAB) 557 (M+H).

Example 36

15 **Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-
L-4-(aminobenzoyl)phenylalanine methyl ester**

Followed the experimental section described for Example 1. *N*-(Toluene-4-sulfonyl)-L-prolyl-L-p-amino-phenylalanine methyl ester (1.75 g, 3.93 mmol) was dissolved in dichloromethane (25 mL) with Et₃N (1.1 eq, 600 mL) and benzoyl chloride (1.1 eq, 860 mL). The title material was
20 isolated as a solid, in 90% yield (1.95 g, 3.55 mmol), mp = 191-193°C.

NMR data was as follows:

¹H NMR (300 MHz, CDCl₃): δ = 7.94 (broad s, 1H), 7.67 (d, 2H, J = 8.31 Hz), 7.71 (d, 2H, J = 8.22 Hz), 7.60 (d, 2H, J = 8.37 Hz), 7.45 (m, 5H),
25 7.34 (d, 2H, J = 8.34 Hz), 7.16 (d, 2H, J = 8.25 Hz), 4.82 (m, 1H), 4.40 (broad s, 1H), 4.05 (m, 1H), 3.77 (s, 3H), 3.40 (m, 1H), 3.23 (m, 1H), 3.09 (m, 2H), 2.42 (s, 3H), 2.02 (m, 1H), 1.56 (m, 3H).

¹³C NMR (75 MHz, CDCl₃): δ = 171.93, 171.46, 144.93, 137.98, 135.45, 133.49, 132.78, 132.44, 130.55, 129.36, 128.43, 127.53, 120.80,
30 62.83, 54.02, 53.11, 50.29, 37.96, 30.31, 24.88, 22.16.

Mass Spectroscopy: (FAB) 550 (M+H).

Example 37

Synthesis of

***N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-chloro)phenylalanine methyl ester**

N-(Toluene-4-sulfonyl)-L-proline (660 mg, 2.3 mmol) was added to
5 12 mL of DMF, at room temperature under N₂. To this was added L-(4-chloro)phenylalanine methyl ester hydrochloride (1.1 eq. 493.3 mg), *N*-methyl morpholine (3.5 eq., 890 mL) and BOP reagent (1.0 eq., 660 mg). The title compound was isolated as an oil in 31% yield (310 mg, 0.7 mmol).

NMR data was as follows:

10 ¹H NMR (300 MHz, CDCl₃): δ = 7.70 (broad d, 2H), 7.35 (m, 2H), 7.25 (m, 2H), 7.11 (m, 2H), 4.82 (m, 1H), 4.05 (m, 1H), 3.78 (s, 3H), 3.35 (m, 1H), 3.25 (m, 1H), 3.05 (m, 2H), 2.45 (s, 3H), 1.52 (m, 3H).

Mass Spectroscopy: (FAB) 433 (M+H).

15

Example 38

Synthesis of

***N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-amino)phenylalanine methyl ester**

N-(Toluene-4-sulfonyl)-L-prolyl-L-(4-nitro)phenylalanine methyl
ester (2.00 g, 4.48 mmol) was dissolved in MeOH (10 mL) with a catalytic
20 amount of 10% Pd on C. The hydrogenation reaction was run at room temperature for 12 hours at 40 psi. Upon filtration of the reaction mixture over Celite, the solvent was evaporated under reduced pressure yielding the title compound as a pink foam in quantitative yields.

NMR data was as follows:

25 ¹H NMR (300 MHz, CDCl₃): δ = 7.68 (d, 2H, J = 8.25 Hz), 7.30 (d, 2H, J = 8.07 Hz), 6.88 (d, 2H, J = 8.25 Hz), 6.57 (d, 2H, J = 8.25 Hz), 4.74 (m, 1H), 4.04 (broad m, 3H), 3.70 (s, 3H), 3.36 (m, 1H), 3.11 (m, 2H), 2.92 (m, 1H), 2.39 (s, 3H), 1.97 (m, 1H), 1.48 (m, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ = 172.14, 171.31, 145.97, 144.86, 133.61, 130.65, 130.51, 128.43, 126.23, 115.79, 111.35, 62.83, 54.16, 52.96, 50.21, 37.68, 30.34, 24.76, 22.16, 14.7.

Mass Spectroscopy: (FAB) 446 (M+H).

5

Example 39

Synthesis of *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-acetamido)phenylalanine methyl ester

10 The title compound was prepared following the experimental procedure described for Example 1 and was isolated as a foam in quantitative yields.

NMR data was as follows:

^1H NMR (300 MHz, CDCl_3): δ = 7.70 (d, 2H, J = 8.10 Hz), 7.65 (m, 2H), 7.33 (d, 2H, J = 8.40 Hz), 7.08 (d, 2H, J = 8.40 Hz), 4.79 (m, 1H), 4.05 (m, 1H), 3.75 (s, 3H), 3.37 (m, 1H), 3.11 (m, 3H), 2.42 (s, 3H), 2.22 (s, 3H), 2.02 (m, 1H), 1.48 (m, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ = 177.61, 171.92, 171.46, 169.07, 144.98, 137.69, 133.41, 132.25, 130.56, 130.32, 128.41, 120.40, 62.83, 54.00, 53.10, 50.28, 45.10, 37.89, 30.34, 25.13, 24.84, 22.17.

20

Mass Spectroscopy: (FAB) 488 (M+H).

Example 40

Synthesis of 25 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-(*N*-benzyl)-histidine methyl ester

N-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiazolidine-4-carboxylic acid was prepared from L-(5,5-dimethyl)thiazolidine-4-carboxylic acid using the procedure described in Method 1. The title compound was prepared using standard coupling procedures to provide a solid, mp = 60-66°C.

30

NMR data was as follows:

¹H NMR (CDCl₃, 300 MHz): δ = 1.17 (s, 3H), 1.30 (s, 3H), 2.43 (s, 3H), 3.09 (m, 2H), 3.67 (s, 3H), 3.92 (s, 1H), 4.45 (d, 1H, J = 10.2 Hz), 4.62 (d, 1H, J = 10.1 Hz), 5.03 (s, 2H), 6.71 (s, 1H), 7.13 (d, 2H, J = 7.7 Hz), 7.29-7.38 (m, 5H), 7.46 (s, 1H), 7.76 (d, 2H, J = 8.1 Hz), 7.93 (d, 1H, J = 7.4 Hz).

¹³C NMR (CDCl₃, 75 MHz): δ = 22.3, 24.9, 29.8, 30.3, 51.1, 51.5, 52.9, 53.0, 55.3, 74.0, 117.9, 128.0, 128.6, 128.9, 129.6, 130.5, 133.0, 136.5, 137.6, 137.9, 145.0, 169.1, 171.9.

Mass Spectroscopy: (FAB+) 557 (M+H).

Example 4

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-4-(3-3'-tolylureido)-L-phenylalanine

The methyl ester was prepared by the reaction of *N*-(toluene-4-sulfonyl)-L-prolyl-L-4-aminophenylalanine with 3-tolylisocyanate (triethylamine, toluene, reflux one hour). The resulting solid was removed by filtration and washed well with EtOAC/Hexane to give the methyl ester as a white solid. The methyl ester was hydrolyzed using 1M LiOH in THF. The title compound was isolated following acid/base work-up as a white solid, mp = 135-140°C.

NMR data was as follows:

¹H NMR (DMSO-d₆, 400 MHz): δ = 12.79 (br s, 1H); 8.55 (s, 1H); 8.50 (s, 1H); 8.02 (d, 1H, J = 7.9Hz); 7.69 (d, 2H, J = 8.3Hz); 7.39 (d, 2H, J = 7.9Hz); 7.33 (d, 2H, J = 8.56Hz); 7.26 (s, 1H); 7.18 (d, 1H, J = 8.4Hz); 7.12 (m, 3H); 6.75 (d, 1H, J = 7.25Hz); 4.43 (m, 1H); 4.11 (dd, 1H, J = 3, 8.1Hz); 3.32 (m, 1H); 3.1 (m, 1H); 3.01 (dd, 1H, J = 5.05, 13.83Hz); 2.91 (dd, 1H, J = 8.45, 13.73Hz); 2.38 (s, 3H); 1.4-1.63 (m, 4H).

IR (KBr, cm⁻¹): 3340, 3290, 3090, 2980, 1730, 1650, 1600, 1550, 1495, 1350, 1290, 1210, 1160, 660.

Mass Spectroscopy: ((+) FAB, m/e (%)) 565 (60 [M+H]⁺).

Example 42

Synthesis of

***N*-(Toluene-4-sulfonyl-L-prolyl-4-[(2,3,3a,7a-tetrahydro-1H-indole-2-carbonyl)-amino]-L-phenylalanine**

5 The *N*-Boc compound was prepared using the procedures described in Method 13 and Method 6. The title compound was then prepared using the procedure described in Method 10.

NMR data was as follows:

10 ¹H NMR (DMSO-d₆): δ = 7.75 (d, 2H), 7.65 (m, 2H), 7.45 (d, 4H), 7.10 (m, 4H), 6.80 (d, 2H), 4.35 (m, 1H), 4.10 (b, 1H), 4.02 (m, 1H), 3.10 (m, 4H), 2.40 (s, 3H), 1.70 (b, 1H), 1.41 (m, 2H).

Mass Spectroscopy: (+) FAB (M+H)⁺ 579

Example 43

15

Synthesis of

***N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-pentylamino)phenylalanine methyl ester**

20 The methyl ester was prepared by reductive amination of *N*-(toluene-4-sulfonyl)-L-prolyl-L-(4-amino)phenylalanine with valeraldehyde (acetic acid, sodium triacetoxyborohydride, methylene chloride, which was stirred at room temperature for one hour). The crude product was purified by flash chromatography (silica, 1:1 EtOAc:hexane) to afford the methyl ester as a white solid, mp = >160°C.

25

Example 44

Synthesis of

***N*-(Toluene-4-sulfonyl)-L-prolyl-L-O-(2-dibenzylamino-ethyl)-tyrosine methyl ester**

30 The title compound was prepared via *O*-alkylation of *N*-(toluene-4-sulfonyl)-L-prolyl-L-tyrosine methyl ester with *N*-(2-chloroethyl)dibenzylamine hydrochloride in refluxing 2-butanone in the presence of potassium carbonate and sodium iodide. The obtained mixture

was chromatographed on SiO₂ in 1% MeOH/CHCl₃ (R_f = 0.75 using 10% MeOH/CHCl₃).

NMR data was as follows:

¹H NMR (DMSO-d₆, 400 Mhz): δ = 1.4-1.6 (4H, m); 2.38 (3H, s);
5 2.75 (2H, t, J=7,7Hz); 2.95 (2H, m); 3.1 (1H, dd, J=6,10,6Hz); 3.33 (1H, dd);
3.6 (3H, s); 3.65 (4H, s); 4.0 (2H, t, J=6,6Hz); 4.1 (1H, t, J=8,8Hz); 4.5 (1H,
t, J=8,8Hz); 6.75 (2H, d, J=10Hz); 7.08 (2H, d, J=10Hz); 7.2-7.35 (10H, m);
7.4 (2H, d, J=10Hz); 7.68 (2H, d, J=10Hz); 8.1 (1H, d, J=10Hz).

MS: +FAB, m/z 670 ([MH]⁺, 45 %), 154 (100%).

10

Example 45

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-L-O-[2-(dibenzylamino)ethyl]-tyrosine

The methyl ester was prepared via *O*-alkylation of *N*-(toluene-4-
15 sulfonyl)-L-prolyl-L-tyrosine methyl ester with *N*-(2-
chloroethyl)dibenzylamine hydrochloride in refluxing 2-butanone in the
presence of potassium carbonate and sodium iodide. The title compound
was prepared using the procedure described in Method 7, and was isolated as
a solid, mp = 106-110°C.

20 NMR data was as follows:

¹H NMR (DMSO-d₆, 400 Mhz): δ = 1.2-1.45 (3H, m); 1.75 (1H, m);
2.38 (3H, s); 2.75 (2H, t, J=6,6Hz); 2.95 (2H, m); 3.1 (1H, dd, J=7,6,7Hz);
3.38 (1H, bs); 3.62 (4H, s); 3.85 (1H, dd, J=6,4,6Hz); 3.95 (1H, t, J=4,4Hz);
3.97 (2H, t, J=8,8Hz); 6.62 (2H, d, J=10Hz); 6.95 (2H, d, J=10Hz); 7.2-7.4
25 (10H, m); 7.41 (2H, d, J=10Hz); 7.62 (1H, d, J=4Hz); 7.75 (2H, d, J=10Hz).

MS: +FAB, m/z 656 ([MH]⁺, 15 %), 154 (100%).

Example 46

Synthesis of

***N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-pentylamino)phenylalanine**

The title compound was prepared from the product of Example 43
5 using the procedure described in Method 6.

NMR data was as follows:

¹H NMR (DMSO-d₆, 400 MHz): δ = 7.73 (d, 2H, J = 8.1Hz); 7.57 (d,
1H, J = 5.7Hz); 7.39 (d, 2H, J = 7.9Hz); 6.76 (d, 2H, J = 8.3Hz); 6.32 (d, 2H,
J = 8.5Hz); 5.14 (t, 1H, J = 5.6Hz); 3.94 (dd, 1H, J = .2, .007Hz); 3.77 (m,
10 1H); 3.18 (m, 2H); 2.90 (m, 4H); 2.38 (s, 3H); 1.73 (m, 1H); 1.41 (m, 5H);
1.29 (m, 4H); .85 (m, 3H).

IR (KBr, cm⁻¹): 3400, 2950, 2910, 2870, 1660, 1620, 1525, 1405,
1350, 1155, 670, 600, 550.

Mass Spectroscopy: ((+) FAB, m/e (%)) 508 (60 [M+ Li]⁺).

15

Example 47

Synthesis of

***N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(4-chlorobenzylamino)-phenylalanine methyl ester**

20 The title compound was prepared by reductive amination of *N*-(toluene-4-sulfonyl)-L-prolyl-L-(4-amino)-phenylalanine methyl ester with 4-chlorobenzaldehyde (acetic acid, sodium triacetoxyborohydride, methylene chloride, stirred at room temperature for 2.5 hours). The crude product was purified by flash chromatography (silica, 1:1 EtOAc:hexane) to afford the
25 title compound as a white solid.

Example 48

Synthesis of

***N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[3-(4-cyanophenyl)-ureido]-phenylalanine methyl ester**

5 The title compound was prepared by the reaction of *N*-(toluene-4-sulfonyl)-L-prolyl-L-(4-amino)-phenylalanine methyl ester with 4-cyanophenylisocyanate (triethylamine, toluene, reflux 3.5 hours). The crude product was purified by flash chromatography (silica, 1:1 EtOAc:hexane) to give the methyl ester as a white solid, mp = 204-206°C.

10

Example 49

Synthesis of

***N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[3-(4-cyanophenyl)-ureido]-phenylalanine**

15 The title compound was prepared from the product of Example 48 using the procedure described in Method 6 as a solid, mp = 163-165°C.

NMR data was as follows:

¹H NMR (DMSO-d₆, 400 MHz): δ = 12.8 (br s, 1H); 9.12 (s, 1H); 8.78 (s, 1H); 8.04 (d, 1H, J = 8.1Hz); 7.69 (m, 4H); 7.6 (d, 2H, J = 9Hz); 7.39 (d, 2H, J = 8.1Hz); 7.35 (d, 2H, J = 8.5Hz); 7.15 (d, 2H, J = 8.5Hz); 7.12 (m, 3H); 4.43 (m, 1H); 4.11 (dd, 1H, J = 3.1, 8.2Hz); 3.29 (m, 1H); 3.06 (m, 2H); 2.92 (dd, 1H, J = 8.4, 13.9Hz); 2.38 (s, 3H); 1.38-1.63 (m, 4H).

IR (KBr, cm⁻¹): 3360, 2220, 1720, 1650, 1590, 1530, 1510, 1410, 1230, 1150, 1090, 830, 670, 595, 550.

25 Mass Spectroscopy: ((-) FAB, m/z (%)) 574 (40 [M-H]⁻).

Example 50

Synthesis of

***N*-(Toluene-4-sulfonyl)-L-prolyl-L-O-(tert-butoxycarbonylmethyl)-tyrosine methyl ester**

30

The title compound was prepared by reaction of *N*-(toluene-4-sulfonyl)-L-prolyl-L-tyrosine methyl ester with t-butyl bromoacetate

(potassium carbonate, DMF, under Argon for 72 hrs). The product was purified by flash column chromatography (silica, 1:1 hexane:EtOAc) to afford the methyl ester as a white solid, mp = 55°C.

5

Example 51

Synthesis of *N*-(Toluene-4-sulfonyl)-L-prolyl-L-*O*- (*tert*-butoxycarbonylmethyl)-tyrosine

The title compound was prepared from the product of Example 50 using the procedure described in Method 6 and was isolated as a solid, mp = 69-70°C.

NMR data was as follows:

¹H NMR (DMSO-*d*₆, 400 MHz): δ = 12.2 (br s, 1H); 8.00 (d, 1H, J = 8.1 Hz); 7.67 (d, 2H, J = 8.2 Hz); 7.38 (d, 2H, J = 7.9 Hz); 7.11 (d, 2H, J = 8.6 Hz); 6.76 (d, 2H, J = 8.5 Hz); 4.5 (s, 2H); 4.4 (m, 1H); 4.07 (m, 1H); 2.8-3.1 (m, 4H); 2.37 (s, 3H); 1.5 (m, 4H); 1.38 (s, 9H).

IR (KBr, cm⁻¹): 3400, 2950, 1750, 1660, 1510, 1340, 1225, 1160, 1075, 660, 575, 525.

Mass Spectroscopy: (ESI, m/e (%)) 545 (100, (M-H)).

20

Example 52

Synthesis of *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[(3*S*)-3, 4-dihydro-isoquinolin-3-yl-aminocarbonyl]-phenylalanine

N-(Toluene-4-sulfonyl)-L-prolyl-L-(4-amino)phenylalanine methyl ester (20 mmol) was taken into CH₂Cl₂ with HOBT, Boc-L-tetrahydro-isoquinoline-3-carboxylic acid (20 mmol), and DCC (24.3 mmol). The mixture was stirred overnight at room temperature, filtered and concentrated in vacuo. The resulting residue was partitioned between 10% citric acid and EtOAc. The organic layer was washed with H₂O, saturated NaHCO₃, and H₂O, dried over Na₂SO₄, and concentrated in vacuo to yield an amorphous

30

solid. The resulting ester was converted to the acid using the procedure described in Method 6. The title compound was then prepared using the procedure described in Method 10 and was isolated as a solid, mp = 145-150°C.

5 NMR data was as follows:

¹H NMR (DMSO-d₆): δ = 8.12 (d, 1H), 7.70 (d, 2H), 7.55 (d, 2H), 7.40 (d, 2H), 7.25 (d, 6H), 4.45 (m, 1H), 4.38 (d, 1H), 4.28 (m, 1H), 4.10 (d, 1H), 3.10 (m, 2H), 2.40 (s, 3H), 1.60 (m, 4H).

Mass Spectroscopy: (FAB) (M+H)⁺ 591 (M + Na)⁺ 613.

10

Example 53

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-4-[3-(3-methoxy-phenyl)-ureido]-L-phenylalanine methyl ester

15 The title compound was prepared by the reaction of *N*-(toluene-4-sulfonyl)-L-prolyl-L-(4-amino)-phenylalanine methyl ester with 3-methoxy phenylisocyanate (triethylamine, toluene, reflux one hour). The resulting solid was removed by filtration and washed with EtOAc/hexane to give the methyl ester as a white solid, mp = 206-209°C.

20

Example 54

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-4-[3-(3-methoxy-phenyl)-ureido]-L-phenylalanine

25 The title compound was prepared from the product of Example 53 using the procedure described in Method 6.

NMR data was as follows:

30 ¹H NMR (DMSO-d₆, 400 MHz): δ = 12.80 (br s, 1H); 8.6 (d, 2H, J = 13.8); 8.03 (d, 1H, J = 7.9Hz); 7.69 (d, 2H, J = 8.1Hz); 7.39 (d, 2H, J = 8.1Hz); 7.33 (d, 2H, J = 8.56Hz); 7.14 (m, 1H); 6.9 (dd, 1H, J = 1.53, 7.9Hz); 6.52 (dd, 1H, J = 2.19, 8.12Hz); 4.42 (m, 1H); 4.11 (dd, 1H, J = 2.96,

8.45Hz); 3.7 (s, 3H); 3.35 (m, 1H); 3.09 (m, 1H); 3.01 (dd, 1H, J = 4.83, 13.6Hz); 2.91 (dd, 1H, J = 8.34, 13.8Hz); 2.48 (s, 3H); 1.41-1.63 (m, 4H).

IR (KBr, cm^{-1}): 3390, 2940, 1655, 1595, 1545, 1500, 1450, 1345, 1320, 1210, 1160, 660, 580, 545.

5 Mass Spectroscopy: ((+) FAB, m/e (%)) 603(30[M+Na]⁺); 581 (10 [M+H]⁺).

Example 55

Synthesis of

10 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-O-(4,5-dihydro-1H-imidazol-2-yl-methyl)-tyrosine

The methyl ester was prepared by reaction of *N*-(toluene-4-sulfonyl)-L-prolyl-L-O-cyanomethyl-tyrosine methyl ester with ethylene diamine (in refluxing methanol under Argon overnight). The product was purified by
15 flash column chromatography (silica, 5% methanol in chloroform) to afford the methyl ester as a white foam. The title compound was prepared using the procedure described in Method 6 and was isolated as a solid, mp = 147-149°C.

NMR data was as follows:

20 ¹H NMR (DMSO-*d*₆, 400 MHz): δ = 7.74 (d, 2H, J = 8.4Hz); 7.61 (d, 1H, J = 5.7Hz); 7.40 (d, 2H, J = 8.2Hz); 6.97 (d, 2H, J = 8.6Hz); 6.75 (m, 2H); 6.51 (br s, 1H); 4.49 (s, 2H); 3.96 (dd, 1H; J = 2.5, 6Hz); 3.82 (dd, 1H, J = 5.1, 9.6Hz); 3.59 (t, 1H, J = 9.7Hz); 3.21 (t, 1H, J = 9.6Hz); 3.04 (m, 4H); 2.39 (s, 3H); 1.70 (m, 1H); 1.35 (m, 3H).

25 IR (KBr, cm^{-1}): 3400, 2900, 1650, 1610, 1510, 1400, 1315, 1245, 1150, 1075, 1040, 700, 600, 550.

Mass Spectroscopy: (ESI, m/e (%)) 515 (100, (M+H)⁺).

Example 56

Synthesis of

***N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(3-propyl-ureido)-phenylalanine**

The methyl ester was prepared by the reaction of *N*-(toluene-4-sulfonyl)-L-prolyl-L-(4-amino)-phenylalanine methyl ester with propyl isocyanate (triethylamine, toluene, reflux 1.25 hours). The crude product was purified by flash chromatography (silica, 1:1 EtOAc:hexane) to give the methyl ester as a white foam. The title compound was prepared using the procedure described in Method 6.

NMR data was as follows:

¹H NMR (DMSO-d₆, 400 MHz): δ = 12.78 (br s, 1H); 8.29 (s, 1H); 7.99 (d, 1H, J = 8.1Hz); 7.68 (d, 2H, J = 8.1Hz); 7.39 (d, 2H, J = 8.1Hz); 7.26 (d, 2H, J = 8.5Hz); 7.06 (d, 2H, J = 8.5Hz); 6.04 (t, 1H, J = 5.7Hz); 4.39 (m, 1H); 4.1 (dd, 1H, J = 2.9, 8.2Hz); 3.3 (m, 1H); 3.09 (m, 1H); 2.99 (m, 3H); 2.87 (dd, 1H, J = 8.34, 13.83Hz); 2.38 (s, 3H); 1.49-1.64 (m, 3H); 1.40 (m, 3H); 0.84 (t, 3H, J = 7.46Hz).

IR (KBr, cm⁻¹): 3590, 3350, 3220, 3050, 2960, 2930, 2860, 1750, 1660, 1630, 1590, 1560, 1540, 1345, 1320, 1160, 660, 590.

Mass Spectroscopy: ((+) FAB, m/e (%)) 539 (40, [M + Na]⁺); 517 (20 [M+H]⁺).

Example 57

Synthesis of

***N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-benzylamino)phenylalanine**

The title compound was prepared from the product of Example 58 using the procedure described in Method 6.

NMR data was as follows:

¹H NMR (DMSO-d₆, 400 MHz): δ 7.72 (d, 2H, J = 8.3 Hz); 7.54 (d, 1H, J = 5.49 Hz); 7.4 (d, 2H, J = 7.9 Hz); 7.27 (m, 4H); 7.17 (m, 1H); 6.72 (d, 2H, J = 8.56 Hz); 6.34 (d, 2H, J = 8.56 Hz); 5.91 (t, 1H, J = 6.15 Hz); 4.17

(d, 2H, J = 6.15 Hz); 3.91 (dd, 1H, J = 2.74, 8.89 Hz); 3.75 (m, 1H); 2.95 (m, 2H); 2.88 (m, 2H); 2.38 (s, 3H); 1.66 (m, 1H); 1.18-1.42 (m, 3H).

IR (KBr, cm^{-1}) 3400, 1655, 1620, 1525, 1410, 1340, 1160, 670.

MS ((+) FAB, m/e (%)) 528 (100 [M + Li]⁺); 522 (15 [M+H]⁺).

5 Anal. Calc'd for $\text{C}_{28}\text{H}_{30}\text{N}_3\text{O}_5\text{S Li } 1.5 \text{ H}_2\text{O}$; C, 60.64; H, 5.90; N, 7.57.

Found: C, 60.60; H, 5.61; N, 7.45.

Example 58

Synthesis of

10

***N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-benzylamino)phenylalanine methyl ester**

The title compound was prepared by reductive amination of *N*-(toluene-4-sulfonyl)-L-prolyl-L-4-aminophenylalanine methyl ester with benzaldehyde (acetic acid, sodium triacetoxyborohydride, methylene chloride, stirred at room temperature overnight). The crude product was purified by flash chromatography (silica, 1:1 EtOAc:hexane) to afford the title compound as a white solid, mp = 53-56°C (0.501 g, 41%).

NMR data was as follows:

¹H NMR (DMSO- d_6 , 400 MHz): δ 8.09 (d, 1H, J = 7.90 Hz); 7.68 (d, 2H, J = 8.34 Hz); 7.39 (d, 2H, J = 7.90 Hz); 7.28 (m, 4H); 7.17 (m, 1H); 6.87 (d, 2H, J = 8.34 Hz); 6.46 (d, 2H, J = 8.56 Hz); 6.12 (t, 1H, J = 6.15 Hz); 4.38 (m, 1H); 4.20 (d, 2H, J = 5.71 Hz); 4.07 (m, 1H); 3.58 (s, 3H); 3.27 (m, 1H); 3.06 (m, 1H); 2.82 (m, 2H); 2.39 (s, 3H); 1.53 (m, 3H); 1.36 (m, 1H).

25 IR (KBr, cm^{-1}) 3400, 2950, 1745, 1675, 1610, 1525, 1450, 1350, 1210, 1100, 680, 595, 550.

MS ((+) FAB, m/e (%)) 536 (70 [M+H]⁺).

Anal. Calc'd for $\text{C}_{29}\text{H}_{33}\text{N}_3\text{O}_5\text{S}$: C, 65.03; H, 6.21; N, 7.84.

Found: C, 64.57; H, 6.10; N, 7.58.

30

Example 59

**Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-L-4-
(4-chlorobenzylamino)-phenylalanine**

5 The methyl ester was prepared by reductive amination of *N*-(toluene-4-sulfonyl)-L-prolyl-L-(4-amino)-phenylalanine methyl ester with 4-chlorobenzaldehyde (acetic acid, sodium triacetoxyborohydride, methylene chloride, stirred at room temperature for 2.5 hours). The crude product was purified by flash chromatography (silica, 1:1 EtOAc:hexane) to afford the methyl ester as a white solid. The title compound was prepared using the
10 procedure described in Method 6.

NMR data was as follows:

¹H NMR (DMSO-d₆, 400 MHz): δ = 7.72 (d, 2H, J = 8.3Hz); 7.53 (d, 1H, J = 5.7Hz); 7.4 (d, 2H, J = 7.9Hz); 7.3 (s, 4H); 6.72 (d, 2H, J = 8.3Hz);
15 6.31 (d, 2H, J = 8.5Hz); 6.0 (m, 1H); 4.16 (d, 2H, J = 6.1Hz); 3.92 (dd, 1H, J = 9, 2.85Hz); 3.75 (m, 1H); 2.91 (m, 4H); 2.38 (s, 3H); 1.65 (m, 1H); 1.35 (m, 1H); 1.18 (m, 2H).

IR (KBr, cm⁻¹): 3400, 1620, 1525, 1410, 1340, 670.

Mass Spectroscopy: (+) FAB, m/e (%) 578 (95, [M + Na]⁺); 562
20 (50, [M + Li]⁺); 556 (40 [M + H]⁺).

Example 60

**Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-L-
(4-chloromethanesulfonylamino)-phenylalanine**

25 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-amino)-phenylalanine methyl ester (1.00g, 2.2 mmol) was dissolved in methylene chloride (2.5 mL) and cooled to -78°C. With stirring, chloromethane sulfonyl chloride (0.34g, 2.2 mmol) was added followed by dropwise addition of pyridine (182 mL, 2.2
30 mmol). The clear solution became yellow, then orange, then finally red upon the chloromethanesulfonyl chloride addition. The solution was allowed to

warm to room temperature and was stirred for 16 hr. The reaction solution was transferred to a 250 mL separatory funnel with CH₂Cl₂ (50 mL) and extracted with 1N HCl (50 mL x 2), brine (50 mL x 2), and water (50 mL). The organic phase was dried (MgSO₄) and the solvent removed to give a red solid which was flash chromatographed (SiO₂, 3:1 CH₂Cl₂:CH₃CN) to yield a white solid. The title compound was prepared using the procedure described in Method 6 and was isolated as a solid, mp = 163-170°C.

NMR data was as follows:

¹H NMR (DMSO-d₆, 400 Mhz): δ = 8.08 (d, 1H, J = 7.7Hz); 7.71 (dd, 4H, J = 14.7Hz, 8.3Hz); 7.51 (d, 1H, J = 5.9Hz); 7.41-7.39 (m, 4H); 6.84-6.82 (m, 2H); 6.78-6.72 (m, 4H); 6.68 (d, 2H, J = 7.5Hz); 4.40 (q, 1H, J = 7.7Hz); 4.18 (s, 3H); 4.19-4.08 (m, 1H); 3.95-3.89 (m, 2H); 3.60 (s, 2H); 3.11-3.04 (m, 2H); 2.95-2.83 (m, 3H); 2.39 (s, 3H); 1.78-1.65 (m, 1H); 1.61-1.56 (m, 3H); 1.42-1.37 (m, 4H).

IR (KBr, cm⁻¹): 3400, broad; 2960; 2850; 1749; 1650; 1510; 1450; 1400; 1350; 1300; 1260; 1160; 1100; 1000; 840; 800; 650; 600; 550.

Mass Spectroscopy: (-) ESI: 542.1 (M-H); 483.8; 442.2; 341.6; 273.8; 202.1; 144.9.

20

Example 61

Synthesis of

N-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-(aminobenzoyl)phenylalanine methyl ester

The title compound was prepared following the procedure outlined for the preparation of Example 36.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.89-7.85 (m, 3H), 7.74 (d, 2H), 7.60-7.47 (m, 5H), 7.29 (d, 2H), 7.21 (d, 2H), 7.02 (d, 1H), 4.89 (m, 1H), 4.56 (d, 1H), 4.37 (d, 1H), 3.85 (s, 1H), 3.75 (s, 3H), 3.12 (m, 2H), 2.44 (s, 3H), 1.18 (s, 3H), 1.08 (s, 3H).

^{13}C NMR (CDCl_3): δ = 171.8, 169.1, 166.3, 145.4, 137.6, 135.8, 133.3, 132.7, 132.5, 130.7, 130.6, 129.4, 128.7, 127.6, 120.7, 74.1, 55.2, 53.9, 53.1, 51.1, 38.4, 29.8, 24.6, 22.3.

5

Example 62

Synthesis of *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)- thiaprolyl-L-4-(benzamido)phenylalanine

The title compound was prepared from the product of Example 61
10 using the procedure described in Method 7.

NMR data was as follows:

^1H NMR (CDCl_3): δ = 8.43 (s, 1H), 7.84 (d, 2H), 7.72 (d, 2H), 7.61 (d, 2H), 7.49-7.20 (m, 7H), 4.93 (q, 1H), 4.55 (d, 1H), 4.37, (d, 1H), 3.92 (s, 1H), 3.15 (m, 2H), 2.42 (s, 3H), 1.19 (s, 3H), 1.08 (s, 3H).

15

^{13}C NMR (CDCl_3): δ = 177.62, 174.35, 169.69, 145.53, 137.73, 135.51, 133.19, 132.44, 132.39, 130.79, 130.63, 129.23, 128.63, 127.82, 121.1, 73.94, 55.13, 53.97, 51.08, 38.02, 29.79, 24.62, 22.24.

Example 63

20

Synthesis of *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)- thiaprolyl-L-tyrosine ethyl ester

The title compound was prepared following the procedure outlined
for the preparation of Example 36.

25

NMR data was as follows:

^1H NMR (CDCl_3): δ = 7.73 (d, 2H), 7.33 (d, 2H), 7.08-7.04 (m, 3H), 6.73 (d, 2H), 6.51 (s, 1H), 4.88 (e, 1H), 4.54 (d, 2H), 4.33 (d, 2H), 1.28 (t, 3H), 4.23 (q, 2H), 3.83 (s, 1H), 3.14-2.93 (m, 2H), 2.43 (s, 3H), 1.03 (s, 3H), 1.02 (s, 3H).

^{13}C NMR (CDCl_3): $\delta = 171.56, 169.44, 155.87, 145.40, 133.16, 131.16, 130.59, 128.66, 127.97, 116.00, 74.01, 62.35, 55.11, 54.16, 51.04, 38.33, 29.79, 24.26, 22.24, 14.67.$

5

Example 64

Synthesis of

N-(Toluene-4-Sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-tyrosine

The title compound was prepared from the product of Example 63 using the procedure described in Method 7.

10

NMR data was as follows:

^1H NMR (CDCl_3): $\delta = 7.96$ (d, 1H), 7.49 (d, 2H), 7.17 (d, 2H), 6.91 (d, 2H), 6.49 (d, 2H), 4.40 (m, 1H), 4.38-4.27 (dd, 2H), 3.83 (s, 1H), 2.95-2.70 (m, 2H), 2.23 (s, 3H), 0.94 (s, 3H), 0.92 (s, 3H).

15

Example 65

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-L-4-[(pyridin-4-yl)methylamino]phenylalanine

The title compound was prepared from the product of Example 66 using the procedure described in Method 6.

20

NMR data was as follows:

^1H NMR ($\text{DMSO}-d_6$, 400 MHz): $\delta = 8.42$ (d, 2H, $J = 5.93\text{Hz}$); 7.72 (d, 2H, $J = 8.34\text{Hz}$); 7.53 (d, 1H, $J = 5.71\text{Hz}$); 7.39 (d, 2H, $J = 7.90\text{Hz}$); 7.28 (d, 2H, $J = 5.93\text{Hz}$); 6.74 (d, 2H, $J = 8.56\text{Hz}$); 6.31 (d, 2H, $J = 8.34\text{Hz}$); 6.07 (t, 1H, $J = 6.26\text{Hz}$); 4.22 (d, 2H, $J = 6.15\text{Hz}$); 3.91 (dd, 1H, $J = 2.85, 8.78\text{Hz}$); 3.77 (dd, 1H, $J = 5.38, 9.99\text{Hz}$); 2.95 (m, 2H); 2.89 (m, 2H); 2.38 (s, 3H); 1.66 (m, 1H); 1.19-1.38 (m, 3H).

25

IR (KBr, cm^{-1}) 3400, 1650, 1610, 1520, 1420, 1340, 1155.

MS ((-) ESI, m/e (%)) 521 (100[M-H] $^+$)

30

Anal. Calc'd for $\text{C}_{27}\text{H}_{29}\text{N}_4\text{O}_5\text{S Li } 2.5 \text{ H}_2\text{O}$: C, 56.47; H, 5.97; N, 9.76.

Found: C, 56.32; H, 5.61; N, 9.64.

Example 66

**Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-L-4-
[(pyridin-4-yl)methylamino]phenylalanine methyl ester**

5 Substituting 4-pyridinecarboxaldehyde for benzaldehyde, and following the method for the preparation of Example 58, gave the title compound.

NMR data was as follows:

10 ¹H NMR (DMSO-d₆, 400 MHz) δ = 8.43 (d, 2H, J = 6.15Hz); 8.10 (d, 1H, J = 7.90 Hz); 7.67 (d, 2H, J = 8.12Hz); 7.39 (d, (2H, J=7.90Hz); 7.28 (d, 2H, J = 6.15Hz); 6.89 (d, 2H, J = 8.56 Hz); 6.43 (d, 2H, J = 8.56); 6.26 (t, 1H, J = 6.26 Hz); 4.38 (m, 1H); 4.26 (d, 2H, J = 6.37Hz); 4.06 (m, 1H); 3.58 (s, 3H); 3.28 (m, 1H); 3.06 (m, 1H); 2.84 (m, 2H); 2.39 (s, 3H), 1.51 (m, 3H); 1.34 (m, 1H).

15 IR (KBr, cm⁻¹) 3400, 2930, 1745, 1675, 1615, 1600, 1520, 1345, 1160, 1090, 1000, 770, 720, 600, 550.

MS ((+) FAB, m/e (%)) 537 (75[m+H]⁺).

Example 67

20 **Synthesis of
N-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-
(pyridin-3-carboxamido)phenylalanine methyl ester**

The title compound was prepared following the procedure outlined for the preparation of Example 36.

25 NMR data was as follows:

¹H NMR (CDCl₃): δ = 9.01 (d, 1H), 8.74 (m, 1H), 8.23 (m, 2H), 7.73 (d, 2H), 7.59 (d, 2H), 7.43 (m, 1H), 7.33 (d, 2H), 7.27 (m, 1H), 7.20 (d, 2H), 4.84 (m, 1H), 4.40-4.32 (dd, 2H), 3.86 (s, 1H), 3.74 (s, 3H), 3.15-3.10 (m, 2H), 2.44 (s, 3H), 1.19 (s, 3H), 1.05 (s, 3H).

^{13}C NMR (CDCl_3): δ = 171.8, 169.2, 164.3, 152.9, 148.5, 145.4, 137.2, 136.1, 133.3, 133.2, 131.3, 130.8, 130.6, 128.6, 124.3, 121.0, 74.1, 55.1, 54.1, 53.0, 51.1, 38.2, 29.8, 24.6, 22.2.

5

Example 68

**Synthesis of
N-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-
thiaprolyl-L-4-(pyridine-3-carboxamido)phenylalanine**

The title compound was prepared from the product of Example 67
10 using the procedure described in Method 7.

NMR data was as follows:

^1H NMR ($\text{CD}_3)_2\text{SO}$): δ = 9.10 (s, 1H), 8.73 (d, 1H), 8.33 (d, 1H), 7.78
(d, 2H), 7.73 (d, 1H), 7.62 (d, 2H), 7.53 (m, 1H), 7.41 (d, 2H), 7.20 (d, 2H),
4.51 (dd, 2H), 4.08-4.03 (m, 2H), 3.00 (m, 2H), 2.39 (s, 3H), 1.19 (s, 3H),
15 1.10 (s, 3H).

^{13}C NMR ($\text{CD}_3)_2\text{SO}$): δ = 173.1, 167.1, 164.1, 152.3, 149.1, 144.3,
137.0, 135.8, 135.2, 134.2, 131.1, 130.3, 130.2, 128.3, 123.8, 120.1, 73.0,
55.9, 54.9, 50.6, 37.5, 29.9, 25.0, 21.4.

20

Example 69

**Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-L-
4-[(pyridin-3-ylmethyl)amino]phenylalanine**

Substituting 3-pyridinecarboxaldehyde for benzaldehyde, and
25 following the method for the preparation of Example 58, gave the title
compound.

NMR data was as follows:

^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ = 8.51 (s, 1H); 8.38 (m, 1H); 7.72
(d, 2H, $J=8.13\text{Hz}$); 7.68 (m, 1H); 7.54 (d, 1H, $J=5.71\text{Hz}$); 7.40 (d, 2H,
30 $J=7.90\text{Hz}$); 7.28 (m, 1H); 6.75 (d, 2H, $J=8.56\text{Hz}$); 6.36 (d, 2H, $J=8.56\text{Hz}$);

5.98 (t, 1H, J=5.27, 9.88Hz); 2.96 (m, 2H); 2.89 (m, 2H); 2.39 (s, 3H); 1.65 (m, 1H); 1.16-1.43 (m, 3H).

IR (KBr, cm^{-1}) 3400, 1670, 1620, 1520, 1400, 1345, 1160, 675, 600.

MS ((+) FAB, m/e (%)) 523 (25[M+H]⁺); 529 (100[M + Li]⁺).

5 Anal. Calc'd for $\text{C}_{27}\text{H}_{29}\text{N}_4\text{O}_5\text{S Li } 2.5 \text{ H}_2\text{O}$: C, 56.47; H, 5.97; N, 9.76.
Found: C, 56.62; H, 5.57; N, 9.69.

Example 70

Synthesis of

10 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)- thiaprolyl-L-4-nitrophenylalanine methyl ester

The title compound was prepared following the procedure outlined for the preparation of Example 36.

NMR data was as follows:

15 ¹H NMR (CDCl_3): δ = 8.14 (d, 2H), 7.74 (d, 2H), 7.41 (d, 2H), 7.35 (d, 2H), 7.10 (d, 1H), 4.94 (m, 1H), 4.58 (d, 1H), 4.33 (d, 1H), 3.82 (s, 1H), 3.76 (s, 3H), 3.25 (m, 2H), 2.44 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H).

¹³C NMR (CDCl_3): δ = 171.3, 169.3, 147.7, 145.6, 144.6, 133.0, 131.0, 130.6, 128.6, 124.2, 74.0, 54.9, 53.6, 53.3, 51.1, 38.7, 29.8, 24.5, 22.3.

20

Example 71

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-L-4-nitrophenylalanine ethyl ester

25 The title compound was prepared following the procedure outlined for the preparation of Example 36.

NMR data was as follows:

30 ¹H NMR (CDCl_3): δ = 8.16 (d, 2H), 7.71 (d, 2H), 7.48 (d, 1H), 7.40-7.31 (m, 4H), 4.87 (q, 1H), 4.24 (q, 2H), 4.07 (m, 1H), 3.44-3.35 (m, 2H), 3.23-3.05 (m, 2H), 2.44 (s, 3H), 2.04 (m, 1H), 1.62-1.44 (m, 3H), 1.30 (t, 3H).

^{13}C NMR (CDCl_3): δ = 171.5, 170.9, 147.6, 145.1, 144.7, 133.2, 130.9, 130.6, 128.4, 124.2, 62.7, 62.6, 53.7, 50.8, 38.4, 30.1, 25.0, 22.2, 14.7.

Example 72

5

Synthesis of *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-methoxybenzamido)phenylalanine ethyl ester

The title compound was prepared following the procedure outlined for the preparation of Example 36.

10

NMR data was as follows:

^1H NMR (CDCl_3): δ = 9.81 (s, 1H), 8.27(d, 1H), 7.71 (d, 2H), 7.60 (d, 2H), 7.49 (t, 1H), 7.37-7.28 (m, 3H), 7.18-7.10 (m, 3H), 7.03 (d, 1H), 4.82 (m, 2H), 4.22 (q, 2H), 4.10-4.04 (m, 4H), 3.40 (m, 1H), 3.30-3.02 (m, 3H), 2.42 (s, 3H), 2.03 (m, 1H), 1.53 (m, 3H), 1.30 (t, 3H).

15

^{13}C NMR (CDCl_3): δ = 171.4, 163.7, 157.8, 144.9, 137.9, 133.9, 133.6, 133.1, 132.4, 130.5, 128.5, 122.3, 120.9, 112.1, 62.9, 62.3, 56.8, 54.1, 50.3, 38.0, 30.5, 24.9, 22.2, 14.7.

Example 73

20

Synthesis of *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-(4-nitro)phenylalanine ethyl ester

The title compound was prepared following the procedure outlined for the preparation of Example 36.

25

NMR data was as follows:

^1H NMR (CDCl_3): δ = 8.12 (d, 2H), 7.73 (d, 2H), 7.42 (d, 2H), 7.34 (d, 2H), 7.12 (d, 1H), 4.92 (m, 1H), 4.57 (d, 1H), 4.33 (d, 1H), 4.20 (q, 2H), 3.83 (s, 1H), 3.33-3.15 (m, 2H), 2.43 (s, 3H), 1.25 (t, 3H), 1.11 (s, 3H), 1.01 (s, 3H).

^{13}C NMR (CDCl_3): δ = 170.8, 169.3, 147.6, 145.5, 144.7, 133.0, 131.1, 130.6, 128.6, 124.2, 74.0, 62.6, 54.9, 53.6, 51.0, 38.8, 29.8, 24.5, 22.2, 14.7.

5

Example 74

Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-bromobenzamido)phenylalanine ethyl ester

The title compound was prepared following the procedure outlined
10 for the preparation of Example 36.

NMR data was as follows:

^1H NMR (CDCl_3): δ = 7.78 (s, 1H), 7.70 (d, 2H), 7.65-7.55 (m, 4H),
7.42-7.29 (m, 5H), 7.16 (d, 2H), 4.81 (m, 1H), 4.23 (q, 2H), 4.06 (m, 1H),
3.43-3.00 (m, 4H), 2.43 (s, 3H), 2.08-1.99 (m, 1H), 1.60-1.45 (m, 3H), 1.30
15 (t, 3H).

^{13}C NMR (CDCl_3): δ = 171.5, 171.3, 166.1, 144.9, 138.3, 137.1,
134.1, 133.5, 133.3, 132.3, 130.6, 130.5, 130.3, 128.5, 128.3, 120.6, 119.8,
62.9, 62.3, 51.0, 50.3, 38.0, 30.4, 24.9, 22.2, 14.7.

20

Example 75

Synthesis of
N-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiamorphyl-L-4-aminophenylalanine ethyl ester

The title compound was prepared following the procedure outlined
25 for the preparation of Example 38.

NMR data was as follows:

^1H NMR (CDCl_3): δ = 7.74 (d, 2H), 7.33 (d, 2H), 6.96 (m, 3H), 6.59
(d, 2H), 4.81 (m, 1H), 4.53 (d, 1H), 4.38 (d, 1H), 4.19 (q, 2H), 3.85 (s, 1H),
3.61 (br s, 2H), 2.98 (m, 2H), 2.44 (s, 3H), 1.26 (t, 3H), 1.17 (s, 3H), 1.10 (s,
30 3H).

¹³C NMR (CDCl₃): δ = 171.5, 168.8, 125.9, 145.3, 133.4, 130.9, 130.5, 128.7, 126.3, 115.8, 74.1, 62.1, 55.3, 54.1, 38.2, 29.8, 24.6, 22.2, 14.7.

Example 76

5

Synthesis of *N*-(Toluene-4-sulfonyl)-L-prolyl- L-4-acetamidophenylalanine ethyl ester

The title compound was prepared following the procedure outlined for the preparation of Example 39.

10

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.69 (d, 2H), 7.52 (s, 1H), 7.42 (d, 2H), 7.38-7.30 (m, 3H), 7.09 (d, 2H), 4.78 (m, 1H), 4.21 (q, 2H), 4.04 (m, 1H), 3.38 (m, 1H), 3.25-2.97 (m, 3H), 2.43 (s, 3H), 2.13 (s, 3H), 2.02 (m, 1H), 1.58-1.44 (m, 3H), 1.28 (t, 3H).

15

¹³C NMR (CDCl₃): δ = 171.4, 169.0, 144.9, 137.6, 133.4, 132.4, 130.6, 130.4, 128.4, 120.4, 62.9, 62.3, 54.0, 50.3, 37.9, 30.4, 25.2, 24.9, 22.2, 14.7.

Example 77

20

Synthesis of *N*-(Toluene-4-sulfonyl)-L-prolyl- L-4-(2-methoxybenzamido)phenylalanine

The title compound was prepared from the product of Example 72 using the procedure described in Method 7.

25

NMR data was as follows:

¹H NMR (CD₃OD): δ = 7.82 (d, 1H), 7.67 (d, 1H), 7.51 (d, 2H), 7.41 (d, 2H), 7.31 (t, 1H), 7.19 (d, 2H), 7.05 (d, 2H), 6.97 (d, 1H), 6.89 (t, 1H), 4.49 (m, 1H), 3.91 (m, 1H), 3.78 (s, 3H), 3.23-2.83 (m, 3H), 2.21 (s, 3H), 1.68-1.28 (m, 4H).

30

Example 78

**Synthesis of
N-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-
thiaprolyl-L-4-acetamidophenylalanine ethyl ester**

5 The title compound was prepared following the procedure outlined
for the preparation of Example 39.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.73 (d, 2H), 7.50 (brs, 1H), 7.42 (d, 2H), 7.33
(d, 2H), 7.15 (d, 2H), 7.02 (d, 1H), 4.84 (m, 1H), 4.53 (d, 1H), 4.35 (d, 1H),
10 4.18 (q, 2H), 3.84 (s, 1H), 3.08 (m, 2H), 2.43 (s, 3H), 2.15 (s, 3H), 1.25 (t,
3H), 1.13 (s, 3H), 1.06 (s, 3H).

¹³C NMR (CDCl₃): δ = 171.3, 169.1, 163.0, 145.4, 137.6, 133.3,
132.4, 130.6, 128.7, 120.4, 112.0, 74.1, 62.3, 55.1, 54.0, 41.1, 38.4, 29.8,
25.2, 24.5, 22.2, 14.7.

15

Example 79

**Synthesis of
N-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-
thiaprolyl-L-4-acetamidophenylalanine**

20 The title compound was prepared from the product of Example 78
using the procedure described in Method 7.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 8.19 (s, 1H), 7.73 (d, 2H), 7.40 (d, 2H), 7.32
(d, 2H), 7.23 (d, 1H), 7.15 (d, 2H), 4.86 (m, 1H), 4.55 (d, 1H), 4.36 (d, 1H),
25 3.92 (s, 1H), 3.10 (m, 2H), 2.42 (s, 3H), 2.10 (s, 3H), 1.19 (s, 3H), 1.07 (s,
3H).

Example 80

Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-
L-4-acetamidophenylalanine Isopropyl Ester

5 The title compound was prepared following the procedure outlined for the preparation of Example 39.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.70 (d, 2H), 7.42 (d, 2H), 7.33 (d, 2H), 7.10 (d, 2H), 5.11-5.03 (m, 1H), 4.80-4.73 (m, 1H), 4.06 (dd, 1H), 3.41-3.36 (m, 10 1H), 3.20 (dd, 1H), 3.12-3.09 (m, 1H), 3.02 (dd, 1H), 2.44 (s, 3H), 2.15 (s, 3H), 2.05-2.01 (m, 1H), 1.58-1.44 (m, 3H), 1.27 (d, 3H).

¹³C NMR (CDCl₃): δ = 170.7, 170.2, 168.3, 144.3, 136.9, 132.9, 131.9, 129.9, 129.9, 127.8, 119.7, 69.5, 62.3, 53.5, 49.7, 37.3, 29.8, 24.6, 24.2, 21.7, 21.7, 21.6.

15

Example 81

Synthesis of
N-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-
L-4-(isonicotinamido)phenylalanine ethyl ester

20 The title compound was prepared following the procedure outlined for the preparation of Example 36.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 8.75 (d, 2H), 8.27 (s, 1H), 7.74-7.68 (m, 4H), 7.59 (d, 2H), 7.33 (d, 2H), 7.22 (d, 2H), 7.08 (d, 1H), 4.86 (m, 1H), 4.54 (d, 25 1H), 4.34 (d, 1H), 4.18 (q, 2H), 3.84 (s, 1H), 3.18-3.03 (m, 2H), 2.43 (s, 3H), 1.26 (t, 3H), 1.26 (t, 3H), 1.15 (s, 3H), 1.04 (s, 3H).

¹³C NMR (CDCl₃): δ = 171.3, 169.1, 164.3, 151.2, 145.4, 142.6, 137.0, 133.4, 133.2, 130.8, 130.6, 128.6, 121.6, 121.0, 74.1, 62.4, 55.1, 54.0, 51.1, 38.4, 29.8, 24.6, 22.2, 14.7.

30

Example 82

**Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-L-4-
(isonicotinamido)phenylalanine ethyl ester**

5 The title compound was prepared following the procedure outlined for the preparation of Example 36.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 8.76 (d, 2H), 8.34 (s, 1H), 7.72 (d, 2H), 7.68 (d, 2H), 7.59 (d, 2H), 7.40 (d, 1H), 7.32 (d, 2H), 7.16 (d, 2H), 4.80 (m, 1H),
10 4.21 (q, 2H), 4.04 (m, 1H), 3.40 (m, 1H), 3.28-3.02 (m, 3H), 2.43 (s, 3H),
2.03 (m, 1H), 1.60-1.42 (m, 3H), 1.29 (t, 3H).

¹³C NMR (CDCl₃): δ = 171.4, 171.3, 164.3, 151.2, 145.0, 142.6, 137.0, 133.5, 133.4, 130.6, 130.6, 128.4, 121.6, 121.0, 62.9, 62.3, 54.1, 52.3, 38.0, 30.3, 24.9, 22.2, 14.7.

15

Example 83

**Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-
L-(π -toluene-4-sulfonyl)histidine methyl ester**

20 L-Prolyl-L-histidine methyl ester was treated with CH₃SO₂Cl and Et₃N in CH₂Cl₂ to give the title compound.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.93 (s, 1H), 7.81 (d, 2H), 7.77 (d, 1H), 7.73 (d, 2H), 7.34 (d, 4H), 7.09 (s, 1H), 4.82 (m, 1H), 4.76-4.09 (dd, 1H), 3.68 (s, 3H), 3.51-3.44 (m, 1H), 3.18-3.08 (m, 3H), 2.45 (s, 3H), 2.41 (s, 3H), 2.10-
25 2.05 (m, 1H), 1.68-1.53 (m, 3H).

¹³C NMR (CDCl₃): δ = 171.1, 171.0, 146.2, 144.2, 140.0, 136.5, 134.8, 133.2, 130.4, 129.9, 127.8, 127.4, 114.8, 62.2, 52.5, 51.9, 49.5, 30.1, 29.9, 24.3, 21.7, 21.6.

30

Example 84

**Synthesis of
N-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-
4-(nicotinamido)phenylalanine ethyl ester**

5 The title compound was prepared following the procedure outlined
for the preparation of Example 36.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 9.06 (s, 1H), 8.76 (d, 1H), 8.22 (d, 1H), 8.14
(s, 1H), 7.73 (d, 2H), 7.59 (d, 2H), 7.45 (t, 1H), 7.33 (d, 2H), 7.23 (d, 2H),
10 7.18 (d, 1H), 4.86 (m, 1H), 4.52 (d, 1H), 4.34 (d, 1H), 4.20 (q, 2H), 3.06-
2.20 (m, 2H), 2.43 (s, 3H), 1.27 (t, 3H), 1.20 (s, 3H), 1.08 (s, 3H).

¹³C NMR (CDCl₃): δ = 171.3, 169.1, 152.9, 148.4, 145.4, 137.1,
136.1, 133.4, 130.8, 130.6, 128.7, 124.3, 120.9, 74.1, 62.3, 55.1, 54.0, 51.1,
38.7, 29.8, 24.6, 22.3, 14.7.

15

Example 85

**Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-L-(O-methyl)tyrosine ethyl ester**

20 The title compound was prepared following the procedure outlined
for the preparation of Example 36.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.71 (d, 2H), 7.32 (m, 3H), 7.06 (d, 2H), 6.80
(d, 2H), 4.77 (m, 1H), 4.21 (q, 1H), 4.18-4.06 (m, 1H), 3.77 (s, 3H), 3.37-
3.34 (m, 1H), 3.20-3.09 (m, 2H), 3.00 (dd, 3H), 2.43 (s, 3H), 1.55-1.46 (m,
25 3H), 1.28 (t, 3H).

¹³C NMR (CDCl₃): δ = 171.5, 171.3, 159.2, 144.9, 133.6, 130.9,
130.5, 128.7, 128.4, 114.4, 62.8, 62.2, 55.8, 54.1, 50.2, 37.7, 30.3, 24.8, 22.3,
14.7.

Example 86

Synthesis of

***N*-(α -Toluenesulfonyl)-L-prolyl-
L-4-(isonicotinamido)phenylalanine ethyl ester**

5 The title compound was prepared following the procedure outlined
for the preparation of Example 36.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 8.72 (d, 2H), 8.45 (s, 1H), 7.69 (d, 2H), 7.55
(d, 2H), 7.45-7.30 (m, 5H), 7.13 (d, 2H), 6.99 (d, 1H), 4.78 (m, 1H), 4.28 (s,
10 2H), 4.18 (q, 2H), 4.03 (m, 1H), 3.23-2.98 (m, 4H), 2.10-1.62 (m, 4H), 1.27
(t, 3H).

¹³C NMR (CDCl₃): δ = 171.6, 174.5, 164.4, 151.1, 142.6, 137.1,
133.3, 131.4, 130.6, 129.5, 129.4, 129.0, 121.6, 121.1, 62.9, 62.4, 57.3, 53.9,
50.1, 37.9, 31.0, 25.5, 14.7.

15

Example 87

Synthesis of

***N*-(Toluene-4-sulfonyl)-L-prolyl-
L-4-(2-bromobenzamido)phenylalanine**

20 The title compound was prepared from the product of Example 74
using the procedure described in Method 7.

NMR data was as follows:

¹H NMR (CD₃OD): δ = 8.01 (brd, 1H), 7.75-7.58 (m, 4H), 7.50-7.33
(m, 4H), 7.24 (d, 2H), 4.70 (m, 1H), 3.50-3.00 (m, 5H), 2.43 (s, 3H), 1.85-
25 1.48 (m, 4H).

Example 88

Synthesis of

***N*-(α -Toluenesulfonyl)-L-prolyl-
L-4-(isonicotinamido)phenylalanine**

30

The title compound was prepared from the product of Example 86
using the procedure described in Method 7.

NMR data was as follows:

¹H NMR (D₂O): δ = 8.45 (d, 2H), 7.50 (d, 2H), 7.26 (d, 2H), 7.18 (s, 5H), 7.05 (d, 2H), 4.29 (m, 1H), 4.10 (m, 2H), 3.83 (m, 1H), 3.20-2.97 (m, 3H), 2.76 (m, 1H), 1.94 (m, 1H), 1.70-1.43 (m, 3H).

5

Example 89

Synthesis of

***N*-(Toluene-4-sulfonyl)-L-(1,1-dioxo)thiamorpholyl-L-4-(2-bromobenzamido))phenylalanine ethyl ester**

10 The title compound was prepared following the procedure outlined for the preparation of Example 36 and the procedure described by Larsson et al., *Acta Chemica Scan.*, 1994, 48, 522.

NMR data was as follows:

15 ¹H NMR (CDCl₃): δ = 8.19 (d, 1H), 7.70 (d, 1H), 7.61-7.50 (m, 5H), 7.36-7.23 (m, 3H), 7.09-7.04 (m, 2H), 6.84 (d, 1/2H), 6.74 (d, 1/2H), 5.10 (d, 1/2H), 4.97 (d, 1/2H), 4.81 (m, 1/2H), 4.66 (m, 1/2H), 4.14 (m, 3H), 3.87 (m, 1H), 3.23-3.74 (m, 6H), 2.41 (s, 3H), 1.22 (t, 3H).

20 ¹³C NMR (CDCl₃): δ = 170.9, 170.7, 166.0, 165.8, 165.1, 164.8, 145.6, 145.5, 137.9, 136.9, 136.7, 135.1, 135.0, 133.4, 132.0, 131.9, 131.5, 130.7, 130.6, 130.0, 130.1, 129.5, 129.4, 127.6, 127.4, 127.2, 120.7, 120.2, 61.8, 55.9, 55.8, 53.5, 53.3, 49.3, 49.2, 48.7, 48.6, 41.8, 41.7, 36.8, 36.3, 21.5, 13.9.

Example 90

25

Synthesis of

***N*-(Toluene-4-sulfonyl)-L-(1,1-dioxo)thiamorpholyl-L-4-(2-bromobenzamido)phenylalanine**

The title compound was prepared from the product of Example 89 using the procedure described in Method 7.

30 NMR data was as follows:

¹H NMR (CD₃OD): δ = 8.12 (d, 0.5H), 7.97 (d, 0.5H), 7.76-7.59 (m, 5.5H), 7.60-7.18 (m, 7H), 5.12 (m, 1H), 4.64 (m, 1H), 4.07 (m, 1H), 3.62 (m, 1H), 3.35 (m, 6H), 2.40 (s, 3H), 2.32-2.14 (m, 3H).

¹³C NMR (CD₃OD): δ = 174.1, 169.7, 169.6, 169.2, 169.1, 146.4,
5 146.2, 140.3, 140.3, 138.7, 138.6, 137.4, 137.2, 134.9, 134.6, 134.3, 132.5,
131.6, 131.5, 131.2, 131.1, 130.0, 129.9, 128.9, 128.7, 128.6, 122.1, 121.8,
120.6, 56.9, 56.8, 54.9, 54.5, 50.8, 50.3, 40.8, 10.4, 37.8, 37.4, 21.6.

Example 91

10

Synthesis of *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)- L-4-(isonicotinamido)phenylalanine

The title compound was prepared from the product of Example 81
using the procedure described in Method 7.

15

Physical data was as follows:

M.p. >200°C;

MS(FAB+) 583(M+H).

Example 92

20

Synthesis of *N*-(α-Toluenesulfonyl)-L-prolyl-L-4- (2-bromobenzamido)phenylalanine ethyl ester

The title compound was prepared following the procedure outlined
for the preparation of Example 36.

25

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.37 (s, 1H, 7.68-7.30 (m, 11H), 7.16 (d, 2H),
6.93 (d, 1H), 4.83 (m, 1H, 4.32 (s, 2H, 4.23 (q, 2H), 4.10 (m, 1H), 3.27-3.03
(m, 5H), 2.10-1.62 (m, 4H), 1.29 (t, 3H).

¹³C NMR (CDCl₃): δ = 166.7, 161.2, 133.4, 132.2, 129.2, 128.1,
30 127.3, 126.4, 125.7, 125.4, 125.6, 124.5, 124.1, 123.4, 115.7, 114.9, 57.8,
57.3, 55.9, 52.4, 48.7, 45.1, 32.8, 26.0, 20.4, 9.6.

Example 93

Synthesis of

***N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-
thiaprolyl-L-tyrosine Isoropyl Ester**

5

The title compound was prepared following the procedure outlined for the preparation of Example 36.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.73 (d, 2H), 7.33 (d, 2H), 7.10 (br d, 1H),
10 7.08 (d, 2H), 6.75 (d, 2H), 5.06 (m, 1H), 4.86 (m, 1H), 4.54 (d, 1H), 4.33 (d,
1H), 3.84 (s, 1H), 3.09-2.97 (m, 2H), 2.43 (s, 3H), 1.23 (dd, 6H), 1.05 (s,
3H), 1.02 (s, 3H).

¹³C NMR (CDCl₃): δ = 170.6, 169.0, 155.3, 144.9, 132.6, 130.6,
130.0, 128.1, 127.2, 115.4, 73.3, 69.6, 65.8, 54.4, 53.6, 50.3, 37.6, 29.0, 23.5,
15 21.5, 21.5.

Example 94

Synthesis of

***N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-
thiaprolyl-L-tyrosine *tert*-Butyl Ester**

20

The title compound was prepared following the procedure outlined for the preparation of Example 36.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.75 (d, 2H), 7.34 (d, 2H), 7.11 (d, 2H), 7.07
25 (d, 1H), 6.76 (d, 2H), 6.62 (br s, 1H), 4.79 (m, 1H), 4.56 (d, 1H), 4.35 (d,
1H), 3.84 (s, 1H), 3.07-2.96 (m, 2H), 2.45 (s, 3H), 1.46 (s, 9H), 1.05 (s, 3H),
1.03 (s, 3H).

¹³C NMR (CDCl₃): δ = 170.1, 168.8, 155.3, 144.9, 132.6, 130.7,
130.0, 128.1, 127.6, 115.3, 82.7, 73.3, 54.5, 54.1, 50.4, 37.8, 29.1, 27.8, 23.5,
30 21.5.

Example 95

Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-L-tyrosine *tert*-Butyl Ester

The title compound was prepared following the procedure outlined
5 for the preparation of Example 36.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.62 (d, 2H), 7.35 (d, 1H), 7.25 (d, 2H), 6.96
(d, 2H), 6.71 (d, 2H), 4.65 (m, 1H), 4.07 (m, 1H), 3.30 (m, 1H), 3.15-2.83
(m, 3H), 2.35 (s, 3H), 1.84 (m, 1H), 1.52-1.34 (m, 13H).

10 ¹³C NMR (CDCl₃): δ = 171.5, 170.0, 155.8, 144.5, 132.8, 130.4,
130.0, 127.8, 127.1, 115.3, 82.5, 62.2, 54.1, 49.5, 37.0, 29.8, 27.7, 23.9, 21.3,
14.0.

Example 96

15 **Synthesis of**
N-(Toluene-4-sulfonyl)-L-prolyl-L-4-
(2-trifluoromethylbenzamido)phenylalanine ethyl ester

The title compound was prepared following the procedure outlined
for the preparation of Example 36.

20 NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.81 (s, 1H), 7.50 - 7.38 (m, 8H), 7.38 (d, 1H),
7.33 (d, 2H), 7.14 (d, 2H), 4.80 (m, 1H), 4.22 (q, 2H), 4.03 (m, 1H), 3.37 (m,
1H), 3.30 - 3.20 (m, 1H), 3.14 - 2.98 (m, 2H), 2.43 (s, 3H), 1.95 (m, 1H),
1.57 - 1.40 (m, 3H), 1.30 (t, 3H).

25 ¹³C NMR (CDCl₃): δ = 171.2, 170.9, 165.8, 144.4, 136.6, 135.7,
132.9, 132.8, 132.2, 130.7, 130.2, 130.0, 130.0, 128.5, 127.9, 126.5, 120.2,
62.1, 61.7, 53.3, 49.6, 37.2, 29.7, 24.0, 21.4, 13.9.

Example 97

Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-
L-4-(2-methylbenzamido)phenylalanine ethyl ester

5 The title compound was prepared following the procedure outlined
for the preparation of Example 36.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.72 (d, 2H), 7.58-7.43 (m, 4H), 7.40-7.20 (m,
7H), 7.15 (d, 2H), 4.82 (m, 1H), 4.24 (q, 2H), 4.08 (m, 1H), 3.43 (m, 1H),
10 3.29-3.03 (m, 3H), 2.50 (s, 3H), 2.44 (s, 3H), 2.05 (m, 1H), 1.55 (m, 3H),
1.31 (t, 3H).

¹³C NMR (CDCl₃): δ = 170.9, 170.9, 144.4, 137.0, 136.5, 133.0,
132.4, 131.3, 130.3, 130.1, 130.0, 127.9, 126.6, 125.9, 119.8, 62.2, 61.6,
53.4, 49.6, 37.3, 29.6, 24.2, 21.4, 19.7, 14.0.

15

Example 98

Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-
L-4-(2-trifluoromethylbenzamido)phenylalanine

20 The title compound was prepared from the product of Example 96
using the procedure described in Method 7.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 8.28 (s, 1H), 7.68-7.40 (m, 9H), 7.33 (d, 2H),
7.17 (d, 2H), 4.84 (m, 1H), 4.05 (m, 1H), 3.44-3.04 (m, 4H), 2.43 (s, 3H),
25 1.90 (m, 1H), 1.49 (m, 3H).

Example 99

Synthesis of
N-(4-Fluorobenzenesulfonyl)-L-thiaprolyl-L-tyrosine *tert*-Butyl Ester

30 The title compound was prepared following the procedure outlined
for the preparation of Example 36.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.87 (m, 2H), 7.23 (m, 3H), 7.03 (d, 2H), 6.73 (d, 2H), 6.29 (s, 1H), 4.68 (m, 1H), 4.56 (m, 2H), 4.10 (d, 1H), 3.29-2.93 (m, 3H), 2.61 (m, 1H), 1.49 (s, 9H).

5 ¹³C NMR (CDCl₃): δ = 169.9, 168.2, 155.4, 132.5, 130.9, 130.7, 127.3, 117.1, 116.8, 115.4, 82.9, 65.0, 54.1, 51.5, 36.8, 33.3, 27.9.

Example 100

10 **Synthesis of**
N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl)-
thiaprolyl-L-tyrosine *tert*-Butyl Ester

The title compound was prepared following the procedure described for the preparation of Example 36.

NMR data was as follows:

15 ¹H NMR (CDCl₃): δ = 7.90 (m, 2H), 7.23 (m, 2H), 7.09 (d, 2H), 6.98 (d, 1H), 6.76 (d, 2H), 4.77 (m, 1H), 4.55 (d, 1H), 4.37 (d, 1H), 3.83 (s, 1H), 3.01 (m, 1H), 1.44 (s, 9H), 1.10 (s, 3H), 1.05 (s, 3H).

¹³C NMR (CDCl₃): δ = 170.1, 168.6, 155.3, 132.0, 131.0, 130.8, 127.7, 116.9, 116.6, 115.3, 82.8, 73.4, 54.6, 54.0, 50.4, 37.8, 29.1, 27.8, 23.5.

20

Example 203

Synthesis of
N-(Toluene-4-sulfonyl)-L-prolyl-L-4-(4-nitro-phenoxy-carbonyloxy)
phenylalanine ethyl ester

25 In a nitrogen atmosphere, Tos-Pro-Tyr ethyl ester was dissolved in CH₂Cl₂ at RT, the flask cooled to 0°C and 4-nitrophenylchloroformate added in one portion. Next, Et₃N was added dropwise slowly, stirred at 0°C for 30 minutes and then at RT for 30 minutes. The reaction mixture was again cooled to 0°C and N,N-dimethylethanolamine was added dropwise. The ice
30 bath was taken away after 10 minutes and the reaction mixture stirred at RT for 3 hours. The reaction mixture was diluted with Et₂O and washed with

10% K₂CO₃ until all yellow color disappeared. Flash chromatography (SiO₂) eluting with 40% EtOAc/hex yielded a white foam in 30% yield.

Example 204

5 **Synthesis of N-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)
thiaprolyl-4-(2-bromobenzamido)-D-phenylalanine t-butyl ester**

The starting (2R)-3-(4-amino-phenyl)-2-[[[(4R)-5,5-dimethyl-3-(toluene-4-sulfonyl)-thiazolidine-4-carbonyl]-amino}-propionic acid tert-butyl ester (230 mg), 2-bromobenzoic acid (100 mg), and
10 4-methylmorpholine (0.19 mL) were dissolved in DMF (5 mL) at 0°C in an ice bath. BOP (229 mg) was added to the solution. The ice bath was removed after 10 minutes. The reaction mixture was stirred at room temperature for 18 hours. Ethyl acetate (20 mL) was added. The mixture was washed with citric acid (5%, 20 mL, 2x) and saturated NaHCO₃ solution
15 (20 mL, 2x), then washed with brine. The solution was dried with MgSO₄. The solvent was evaporated *in vacuo* and the residue was purified using HPLC (reverse phase, 65-95% CH₃OH/water). The retention time was 13 minutes. The desired product was freeze dried to give 181 mg of a white solid. MP: 92-93°C

20

Example 205

Synthesis of N-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-4-(2-bromobenzamido)-L-phenylalanine t-butyl ester

The starting (2S)-3-(4-amino-phenyl)-2-[[[(4R)-5,5-dimethyl-3-(toluene-4-sulfonyl)-thiazolidine-4-carbonyl]-amino}-propionic acid
25 tert-butyl ester (230 mg), 2-bromobenzoic acid (100 mg), and 4-methylmorpholine (0.19 mL) were dissolved in DMF (5 mL) at 0°C in an ice bath. BOP (229 mg) was added to the solution. The ice bath was removed after 10 minutes. The reaction mixture was stirred at room
30 temperature for 18 hours. Ethyl acetate (20 mL) was added. The mixture

was washed with citric acid (5%, 20 mL, 2x) and saturated NaHCO₃ solution (20 mL, 2x), then washed with brine. The solution was dried with MgSO₄. The solvent was evaporated *in vacuo* and the residue was purified using HPLC (reverse phase, 65-95% CH₃OH/water). The retention time was 13.5 minutes. The desired product was freeze dried to give 27 mg of the title compound as a white solid. MP: 92-93°C

Example 207

10 **Synthesis of N-(Toluene-4-sulfonyl)-L-prolyl-4-(1-H, 2-oxo-3-methyltetrahydropyrimidin-1-yl)-L-phenylalanine**

The title compound was prepared from the corresponding t-butyl ester using the procedure described in Method 11.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.73 (d, 2H), 7.58 (d, 1H), 7.34 (d, 2H), 7.21 (d, 2H), 7.17 (d, 2H), 4.79 (q, 1H), 4.15 - 4.11 (m, 1H), 3.68 - 3.63 (m, 2H), 3.48 - 3.39 (m, 3H), 3.27 (dd, 1H), 3.17 (dd, 1H), 3.15 - 3.07 (m, 1H), 2.99 (s, 3H), 2.43 (s, 3H), 2.16 - 2.08 (m, 2H), 2.00 - 1.98 (m, 1H).
¹³C NMR (CDCl₃): δ = 173.4, 172.2, 164.2, 156.4, 144.4, 142.5, 134.1, 133.0, 130.2, 130.0, 127.9, 126.2, 62.1, 53.4, 49.5, 48.9, 47.9, 36.5, 35.9, 30.2, 24.2, 22.0, 21.4.

Example 212

25 **N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl) thiaprolyl-L-3-chloro-4-hydroxyphenylalanine Isopropyl Ester**

The compound was prepared following the procedure described for the preparation of Example 36 employing N-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl, thiaproline (prepared according to Method 8 and 3-chloro-L-

tyrosine isopropyl ester (prepared from commercially available 3-chloro-L-tyrosine and isopropyl alcohol in the presence of anhydrous HCl).

MS:(-) ESI [M-H]⁺ 557

HPLC: 96.8%

5

Example 214

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-4-(2-methoxyphenyl)-L-phenylalanine

The title compound was prepared from the corresponding t-butyl ester using the procedure described in Method 11.

10

NMR data was as follows:

¹H NMR (CD₃OD): δ = 7.70 (m, 2H), 7.36 (m, 4H), 7.22 (m, 4H), 6.98 (m, 2H), 4.75 (m, 1H), 4.10 (m, 1H), 3.71 (s, 3H), 3.29 (m, 2H), 3.11 (m, 2H), 2.39 (s, 3H), 1.75 (m, 1H), 1.53 (m, 3H).

15

¹³C NMR (CD₃OD): δ = 174.4, 174.2, 158.1, 145.9, 138.9, 136.7, 135.1, 131.2, 130.9, 130.8, 130.2, 129.9, 129.1, 122.0, 112.6, 63.3, 55.9, 54.6, 50.5, 37.9, 31.5, 25.2, 21.4.

Example 215

20

Synthesis of

N-(Toluene-4-sulfonyl)-L-prolyl-4-(2-methoxyphenyl)-L-phenylalanine

The title compound was prepared from the corresponding t-butyl ester using the procedure described in Method 11.

NMR data was as follows:

25

¹H NMR (CDCl₃): δ 8.41 (d, 1H), 8.21 (s, 1H), 8.03 (d, 1H), 7.98 (s, 1H), 7.74 (d, 2H), 7.39 (d, 1H), 7.33 (d, 2H), 4.72-4.68 (m, 1H), 4.17-4.13 (m, 1H), 3.54-3.34 (m, 3H), 3.20-3.12 (m, 1H), 2.82 (s, 6H), 2.43 (s, 3H), 2.09-2.04 (m, 1H), 1.79-1.59 (m, 3H).

^{13}C NMR (CDCl_3): δ = 173.7, 171.8, 154.5, 147.2, 144.4, 137.8, 135.5, 133.2, 130.1, 127.9, 126.4, 62.2, 53.0, 49.5, 38.5, 36.0, 30.3, 24.4, 21.4.

5

Example 216

N-(Toluene-4-sulfonyl)-L-prolyl-4-(N,N-dimethylsulfamyl)-L-phenylalanine

The title compound was prepared from the corresponding tert-butyl ester using the procedure described in Method 11.

10

NMR data was as follows:

^1H NMR (CDCl_3): δ = 7.71 (d, 2H), 7.58 (d, 1H), 7.49 (bs, 1H), 7.34 (d, 2H), 7.16 (d, 2H), 7.12 (d, 2H), 4.90 - 4.83 (m, 1H), 4.13 - 4.09 (m, 1H), 3.46 - 3.40 (m, 1H), 3.28 (dd, 1H), 3.15 - 3.04 (m, 2H), 2.77 (s, 6H), 2.43 (s, 3H), 1.93 - 1.88 (m, 1H), 1.54 - 1.45 (m, 3H).

15

^{13}C NMR (CDCl_3): δ = 173.7, 172.0, 144.7, 136.6, 132.6, 132.1, 130.4, 130.2, 127.9, 120.3, 62.2, 53.3, 49.7, 38.0, 36.8, 29.9, 24.1, 21.4.

Example 217

Synthesis of

20

N-(Toluene-4-sulfonyl)-L-prolyl-(N1,N1,N2-trimethylsulfamyl)-L-phenylalanine

The title compound was prepared from the corresponding tert-butyl ester using the procedure described in Method 11.

NMR data was as follows:

25

^1H NMR (CDCl_3): δ = 7.71 (d, 2H), 7.49 (d, 1H), 7.35 (d, 4H), 7.24 (d, 2H), 4.89 - 4.82 (m, 1H), 4.10 - 4.07 (m, 1H), 3.41 - 3.31 (m, 2H), 3.22 (s, 3H), 3.16 - 3.06 (m, 2H), 2.76 (s, 6H), 2.44 (s, 3H), 1.98 - 1.95 (m, 1H), 1.55 - 1.38 (m, 3H).

^{13}C NMR (CDCl_3): δ = 173.7, 171.8, 144.6, 141.7, 135.1, 132.7, 130.2, 103.1, 127.9, 126.6, 62.2, 53.2, 49.6, 39.4, 38.2, 36.7, 29.6, 24.1, 21.5.

30

Example 220

Synthesis of

**N-[4-(3,3-Dimethyl-ureido)-benzenesulfonyl]-L-prolyl-(4-hydroxy)-
L-phenylalanine isopropyl ester**

- 5 The reaction vessel was flushed with N₂, Pd/C was added to the flask and wet with iso-PrOH. Next, the nitro compound was added to the flask in iso- PrOH and a balloon filled with H₂ was attached to the flask. The N₂ was vacuumed out, H₂ added, evacuated, and H₂ added again. The reaction was complete in 2 hours; diluted with iso-PrOH and filtered through Celite and
- 10 evaporated to dryness. Flash chromatography (SiO₂) diluting with 1% MeOH/CH₂Cl₂ yielded a white solid in 62% yield of the lower R_f from the separation.

Example 225

Synthesis of

**N-(Toluene-4-sulfonyl)-L-prolyl-4-(N,N-dimethylaminocarbonylmethyl)-
L-phenylalanine**

15 The title compound was prepared from the product of Example 233 using the procedure described in Method 11.

- 20 NMR data was as follows:

¹H NMR (CD₃OD): δ = 8.04 (d, 1H), 7.70 (d, 2H), 7.40 (d, 2H), 7.20 (m, 4H), 4.99 (bs, 1H), 4.70 (m, 1H), 4.10 (m, 1H), 3.69 (s, 2H), 3.40 (m, 1H), 3.20 (m, 1H), 3.04 (m, 2H), 3.01 (s, 3H), 2.92 (s, 3H), 2.41 (s, 3H), 1.80 (m, 1H), 1.62 (m, 3H).

- 25 ¹³C NMR (CD₃OD): δ = 174.2, 174.1, 173.9, 145.8, 136.8, 135.0, 131.2, 131.0, 130.0, 129.1, 63.2, 54.7, 54.6, 50.5, 41.0, 38.3, 37.7, 35.9, 31.6, 25.2, 21.5.

Example 226

Synthesis of

N-(1-Methylimidazol-4-sulfonyl)-L-prolyl-(4-hydroxyl)-L-phenylalanine isopropyl ester

5 The compound was prepared by BOP coupling of
1-methylimidazole-4-sulfonyl-Pro with Tyr-isopropyl ester. The crude
product was purified by flash chromatography (silica, 95:3:2
EtOAc:EtOH:Et₃N) to afford a white solid, m.p. = 159-162°C. (2.03g, 65%).
MS((+)ESI, m/z (%)) 465 (100 [M+H]⁺).

10

Example 227

Synthesis of

**N-(Toluene-4-sulfonyl)-L-prolyl-4-(2,4,5-trioxo-3-phenyltetrahydro
imidazol-1-yl)-L-phenylalanine isopropyl ester**

15 The compound was prepared by treatment of N-(toluene-4-sulfonyl)-
L-prolyl-4-[(phenyl ureido)-tetrahydroimidazol-1-yl]-L-phenylalanine
isopropyl ester with oxalyl chloride in methylene chloride. The crude
product was purified by flash chromatography (silica, 3:2 Hex:EtOAc) to
afford a white solid. (0.490g, 49%).
20 MS((+)ESI, m/z (%)) 647 (15 [M+H]⁺); 664 (100[M+NH₄]⁺).

Example 229

**N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl) thiaprolyl-L-3-chloro-
4-tert-butoxy-phenylalanine tert-Butyl Ester**

25

The compound was prepared according to the procedure described in
Example 36. The required 3-chloro-O-*tert*-butyl-L-tyrosine *tert*-butyl ester
was prepared from 3-chloro-L-tyrosine and iso-butylene in the presence of
one equivalent of sulfuric acid and used without further purification.

30 MS(+)ESI [M+H]⁺ 629 [M+NH₄]⁺ 646.

Example 231

**N-[2-(N-2,10-camphorsultamyl) acetyl]
-L-3-chloro-4-hydroxyphenylalanine Isopropyl Ester**

5 The above compound was prepared by the following steps:

**Step 1: Preparation of N-(tert-butoxycarbonylmethyl)
camphorsultam**

 Camphorsultam (3g, 14 mmole) in DMF (25 ml) was mixed with
NaH (1.1 equiv.) for 15 minutes, then tert-butyl bromoacetate (2.5 ml) was
10 added and the reaction mixture was stirred overnight. The solvent was
evaporated to dryness and the residue was partitioned between aq-citric
acid and EtoAc. The organic layer was washed with sat. aq. NaHCO₃, and
water, dried and evaporated to give the ester. (3.5 g)

15 **Step 2: Preparation of N-(carboxymethyl) camphorsultam**

 The ester (3.3g) was converted to the acid according to Method 17.
MS (-)ESI [M-H]⁻ 272

20 **Step 3: Preparation of N-[2-(N-2,10-camphorsultamyl) acetyl]-
L-3-chloro-4-hydroxyphenylalanine Isopropyl Ester**

 The titled compound was prepared by amide bond formation
according to a method similar to Example 52.

MS:(+)ESI [M+H]⁺ 513

HPLC: 99.4%

25

Example 236

**Synthesis of
N-(4-Fluorobenzenesulfonyl)-L-prolyl-4-hydroxy-L-phenylalanine
t-butyl ester**

30 The compound was prepared using the procedure described in
Method 12. The crude product was purified by flash column

chromatography (silica, hexane:EtOAc 1:1) to give the title compound as a white foam (580 mg, 64%).

MS (+)ESI, [M+H]⁺ @ m/z 493 [M+NH₄]⁺ @ m/z 510

5

Example 237

Synthesis of N-(4-Fluorobenzenesulfonyl)-L-prolyl-4-hydroxy-L-phenylalanine isopropyl ester

The compound was prepared using the procedure described in

10 Method 12. The crude product was purified by flash column chromatography (silica, hexane:EtOAc 1:1) (380 mg, 43%).

MS (+)ESI, [M+H]⁺ @ m/z 479 (100%) [M+NH₄]⁺ @ m/z 496

Example 238

15

Synthesis of N-(1-Methylimidazol-4-sulfonyl)-L-prolyl-4-hydroxy-L-phenylalanine t-butyl ester

The compound was prepared by BOP coupling of
1-methylimidazole-4-sulfonyl-Pro with Tyr-t-butyl ester. The crude product
20 was purified by flash chromatography (silica, 95:3:2 EtOAc: EtOH:Et₃N) to afford a white solid. (1.21 g, 66%)

MS ((+)ESI, m/z (%)) 479 (100 [M+H]⁺)

Example 239

25

Synthesis of N-(Pyridine-3-sulfonyl)-L-prolyl-4-hydroxy-L-phenylalanine t-butyl ester

The compound was prepared by BOP coupling of
3-pyridinesulfonyl-Pro with Tyr-t-butyl ester. The crude product was
purified by flash chromatography (silica, 95:3:2 EtOAc: EtOH:Et₃N) to
30 afford a pale orange foam. (0.930g, 95%)

MS ((+)ESI, m/z (%)) 476 (100 [M+H]⁺)

Example 240

Synthesis of N-(Toluene-4-sulfonyl)-L-prolyl-4-(methanesulfonamido)-L-phenylalanine

To a solution of 3-(4-methanesulfonamino-phenyl)-
5 2-[[1-(toluene-4-sulfonyl)-pyrrolidine-2-carbonyl]-amino]-propionic acid
methyl ester (0.250 g, 0.477 mmol) in THF (1.0 mL) was added 1N LiOH
(955 mL, 0.955 mmol) and the clear solution was stirred at 25°C, under
nitrogen, for 16 h. The reaction solution was then diluted with additional
water (50mL) and washed with diethyl ether (25 mL). The aqueous layer was
10 lyophilized to afford a fluffy white solid (0.216 g, 87%).
MS (-ESI): 508 [M - 1]-

Example 242

**Synthesis of
15 N-(Toluene-4-sulfonyl)-L-prolyl-4-(2,4,5-trioxo-3-(3-chlorophenyl)-tetra
hydroimidazol-1-yl)-L-phenylalanine benzyl ester**

The compound was prepared by treatment of N-(toluene-4-sulfonyl)-
L-prolyl-4-[(3-chlorophenyl ureido)-tetrahydroimidazol-1-yl]-L-
phenylalanine isopropyl ester with oxalyl chloride in methylene chloride.
20 The crude product was purified by flash chromatography (silica, 3:2 Hex:
EtOAc) to afford a white solid. (0.410g, 50%).
MS ((+)ESI, m/z (%) 746 (100[M+H]+) (746/748 1Cl)

Certain of the above exemplified compounds as well as certain other
25 compounds which can be prepared by the methods described above include
those set forth in Tables IA and IB above.

Example 244

***In vitro* Assay For Determining Binding of
Candidate Compounds to VLA-4**

An *in vitro* assay was used to assess binding of candidate compounds
5 to $\alpha_4\beta_1$ integrin. Compounds which bind in this assay can be used to assess
VCAM-1 levels in biological samples by conventional assays (e.g.,
competitive binding assays). This assay is sensitive to IC_{50} values as low as
about 1nM.

10 The activity of $\alpha_4\beta_1$ integrin was measured by the interaction of
soluble VCAM-1 with Jurkat cells (e.g., American Type Culture Collection
Nos. TIB 152, TIB 153, and CRL 8163), a human T-cell line which
expresses high levels of $\alpha_4\beta_1$ integrin. VCAM-1 interacts with the cell
surface in an $\alpha_4\beta_1$ integrin-dependent fashion (Yednock, et al. *J. Biol. Chem.*,
15 1995, 270:28740).

Recombinant soluble VCAM-1 was expressed as a chimeric fusion
protein containing the seven extracellular domains of VCAM-1 on the N-
terminus and the human IgG₁ heavy chain constant region on the C-terminus.
20 The VCAM-1 fusion protein was made and purified by the manner described
by Yednock, *supra*.

Jurkat cells were grown in RPMI 1640 supplemented with 10% fetal
bovine serum, penicillin, streptomycin and glutamine as described by
25 Yednock, *supra*.

Jurkat cells were incubated with 1.5 mM $MnCl_2$ and 5 $\mu g/mL$ 15/7
antibody for 30 minutes on ice. Mn^{+2} activates the receptor to enhance
ligand binding, and 15/7 is a monoclonal antibody that recognizes an
30 activated/ligand-occupied conformation of $\alpha_4\beta_1$ integrin and locks the

molecule into this conformation thereby stabilizing the VCAM-1/ $\alpha_4\beta_1$ integrin interaction. Yednock, et al., *supra*. Antibodies similar to the 15/7 antibody have been prepared by other investigators (Luque, et al, 1996, J. Biol. Chem. 271:11067) and may be used in this assay.

5

Cells were then incubated for 30 minutes at room temperature with candidate compounds, in various concentrations ranging from 66 μ M to 0.01 μ M using a standard 5-point serial dilution. 15 μ L soluble recombinant VCAM-1 fusion protein was then added to Jurkat cells and incubated for 30 minutes on ice. (Yednock et al., *supra*).

10

Cells were then washed two times and resuspended in PE-conjugated goat F(ab')₂ anti-mouse IgG Fc (Immunotech, Westbrook, ME) at 1:200 and incubated on ice, in the dark, for 30 minutes. Cells were washed twice and analyzed with a standard fluorescence activated cell sorter ("FACS") analysis as described in Yednock, et al., *supra*.

15

Compounds having an IC₅₀ of less than about 15 μ M possess a suitable binding affinity to $\alpha_4\beta_1$.

20

When tested in this assay, each of the compounds in Examples 1-243 has an IC₅₀ of 15 μ M or less.

Example 245

25

In vitro Saturation Assay For Determining Binding of Candidate Compounds to $\alpha_4\beta_1$

The following describes an *in vitro* assay to determine the plasma levels needed for a compound to be active in the Experimental Autoimmune Encephalomyelitis ("EAE") model, described in the next example, or in other *in vivo* models. -

30

Log-growth Jurkat cells are washed and resuspended in normal animal plasma containing 20 µg/ml of the 15/7 antibody (described in the above example).

5 The Jurkat cells are diluted two-fold into either normal plasma samples containing known candidate compound amounts in various concentrations ranging from 66 µM to 0.01 µM, using a standard 12 point serial dilution for a standard curve, or into plasma samples obtained from the peripheral blood of candidate compound-treated animals.

10

Cells are then incubated for 30 minutes at room temperature, washed twice with phosphate-buffered saline ("PBS") containing 2% fetal bovine serum and 1mM each of calcium chloride and magnesium chloride (assay medium) to remove unbound 15/7 antibody.

15

The cells are then exposed to phycoerythrin-conjugated goat F(ab')₂ anti-mouse IgG Fc (Immunotech, Westbrook, ME), which has been adsorbed for any non-specific cross-reactivity by co-incubation with 5% serum from the animal species being studied, at 1:200 and incubated in the dark at 4°C
20 for 30 minutes.

Cells are washed twice with assay medium and resuspended in the same. They are then analyzed with a standard fluorescence activated cell sorter ("FACS") analysis as described in Yednock et al. J. Biol. Chem., 1995,
25 270:28740.

The data is then graphed as fluorescence versus dose, e.g., in a normal dose-response fashion. The dose levels that result in the upper plateau of the curve represent the levels needed to obtain efficacy in an *in vivo* model.
30

This assay may also be used to determine the plasma levels needed to saturate the binding sites of other integrins, such as the $\alpha_9\beta_1$ integrin, which is the integrin most closely related $\alpha_4\beta_1$ (Palmer et al, 1993, *J. Cell Bio.*, 123:1289). Such binding is predictive of *in vivo* utility for inflammatory
5 conditions mediated by $\alpha_9\beta_1$ integrin, including by way of example, airway hyper-responsiveness and occlusion that occurs with chronic asthma, smooth muscle cell proliferation in atherosclerosis, vascular occlusion following angioplasty, fibrosis and glomerular scarring as a result of renal disease, aortic stenosis, hypertrophy of synovial membranes in rheumatoid arthritis,
10 and inflammation and scarring that occur with the progression of ulcerative colitis and Crohn's disease.

Accordingly, the above-described assay may be performed with a human colon carcinoma cell line, SW 480 (ATTC #CCL228) transfected
15 with cDNA encoding α_9 integrin (Yokosaki et al., 1994, *J. Biol. Chem.*, 269:26691), in place of the Jurkat cells, to measure the binding of the $\alpha_9\beta_1$ integrin. As a control, SW 480 cells which express other α and β_1 subunits may be used.

20 Using a conventional oral formulation, compounds of this invention would be active in this model.

Example 246

In vivo Evaluation

25 The standard multiple sclerosis model, Experimental Autoimmune (or Allergic) Encephalomyelitis ("EAE"), was used to determine the effect of candidate compounds to reduce motor impairment in rats or guinea pigs. Reduction in motor impairment is based on blocking adhesion between leukocytes and the endothelium and correlates with anti-inflammatory
30 activity in the candidate compound. This model has been previously

described by Keszthelyi et al., *Neurology*, 1996, 47:1053-1059, and measures the delay of onset of disease.

Brains and spinal cords of adult Hartley guinea pigs were
5 homogenized in an equal volume of phosphate-buffered saline. An equal volume of Freund's complete adjuvant (100 mg *mycobacterium tuberculosis* plus 10 ml Freund's incomplete adjuvant) was added to the homogenate. The mixture was emulsified by circulating it repeatedly through a 20 ml syringe with a peristaltic pump for about 20 minutes.

10

Female Lewis rats (2-3 months old, 170-220 g) or Hartley guinea pigs (20 day old, 180-200 g) were anesthetized with isoflurane and three injections of the emulsion, 0.1 ml each, were made in each flank. Motor impairment onset is seen in approximately 9 days.

15

Candidate compound treatment began on Day 8, just before onset of symptoms. Compounds were administered subcutaneously ("SC"), orally ("PO") or intraperitoneally ("IP"). Doses were given in a range of 10mg/kg to 200 mg/kg, bid, for five days, with typical dosing of 10 to 100 mg/kg SC,
20 10 to 50 mg/kg PO, and 10 to 100 mg/kg IP.

Antibody GG5/3 against $\alpha_5\beta_1$ integrin (Keszthelyi et al., *Neurology*, 1996, 47:1053-1059), which delays the onset of symptoms, was used as a positive control and was injected subcutaneously at 3 mg/kg on Day 8 and
25 11.

Body weight and motor impairment were measured daily. Motor impairment was rated with the following clinical score:

30

	0	no change
	1	tail weakness or paralysis
	2	hindlimb weakness
	3	hindlimb paralysis
5	4	moribund or dead

A candidate compound was considered active if it delayed the onset of symptoms, e.g., produced clinical scores no greater than 2 or slowed body weight loss as compared to the control.

When tested in this *in vivo* assay, the compounds of Examples 10 and 27 were active.

15

Example 247

***In vivo* Evaluation - Asthma**

Inflammatory conditions mediated by $\alpha_4\beta_1$ integrin include, for example, airway hyper-responsiveness and occlusion that occurs with chronic asthma. The following describes an asthma model which can be used to study the *in vivo* effects of the compounds of this invention for use in treating asthma.

Following the procedures described by Abraham et al, *J. Clin. Invest.* 93:776-787 (1994) and Abraham et al, *Am J. Respir Crit Care Med.* 156:696-703 (1997), both of which are incorporated by reference in their entirety, compounds of this invention are formulated into an aerosol and administered to sheep which are hypersensitive to *Ascaris suum* antigen. Compounds which decrease the early antigen-induced bronchial response and/or block the late-phase airway response, e.g., have a protective effect against antigen-induced late responses and airway hyper-responsiveness ("AHR"), are considered to be active in this model.

Allergic sheep which are shown to develop both early and late bronchial responses to inhaled *Ascaris suum* antigen are used to study the airway effects of the candidate compounds. Following topical anesthesia of the nasal passages with 2% lidocaine, a balloon catheter is advanced through one nostril into the lower esophagus. The animals are then intubated with a cuffed endotracheal tube through the other nostril with a flexible fiberoptic bronchoscope as a guide.

Pleural pressure is estimated according to Abraham (1994). Aerosols (see formulation below) are generated using a disposable medical nebulizer that provides an aerosol with a mass median aerodynamic diameter of 3.2 μm as determined with an Andersen cascade impactor. The nebulizer is connected to a dosimeter system consisting of a solenoid valve and a source of compressed air (20 psi). The output of the nebulizer is directed into a plastic T-piece, one end of which is connected to the inspiratory port of a piston respirator. The solenoid valve is activated for 1 second at the beginning of the inspiratory cycle of the respirator. Aerosols are delivered at V_T of 500 ml and a rate of 20 breaths/minute. A 0.5% sodium bicarbonate solution only is used as a control.

20

To assess bronchial responsiveness, cumulative concentration-response curves to carbachol can be generated according to Abraham (1994). Bronchial biopsies can be taken prior to and following the initiation of treatment and 24 hours after antigen challenge. Bronchial biopsies can be preformed according to Abraham (1994).

25

An *in vitro* adhesion study of alveolar macrophages can also be performed according to Abraham (1994), and a percentage of adherent cells is calculated.

30

Aerosol Formulation

A solution of the candidate compound in 0.5% sodium bicarbonate/saline (w/v) at a concentration of 30.0 mg/mL is prepared using the following procedure:

5

A. Preparation of 100.0 mL of 0.5%
Sodium Bicarbonate / Saline Stock Solution

10	Ingredient	Gram / 100.0 mL	Final Concentration
	Sodium Bicarbonate	0.5 g	0.5%
	Saline	q.s. ad 100.0 mL	q.s. ad 100%

Procedure:

1. Add 0.5g sodium bicarbonate into a 100 mL volumetric flask.
- 15 2. Add approximately 90.0 mL saline and sonicate until dissolved.
3. Q.S. to 100.0 mL with saline and mix thoroughly.

20 B. Preparation of 30.0 mg/mL Candidate Compound: 10.0 mL

25	Ingredient	Gram / 10.0 mL	Final Concentration
	Candidate Compound	0.300 g	30.0 mg/mL
	0.5% Sodium Bicarbonate / Saline Stock Solution	q.s. ad 10.0 mL	q.s ad 100%

Procedure:

1. Add 0.300 g of the candidate compound into a 10.0 mL volumetric flask.
2. Add approximately 9.7 mL of 0.5% sodium bicarbonate /
30 saline stock solution.

3. Sonicate until the candidate compound is completely dissolved.

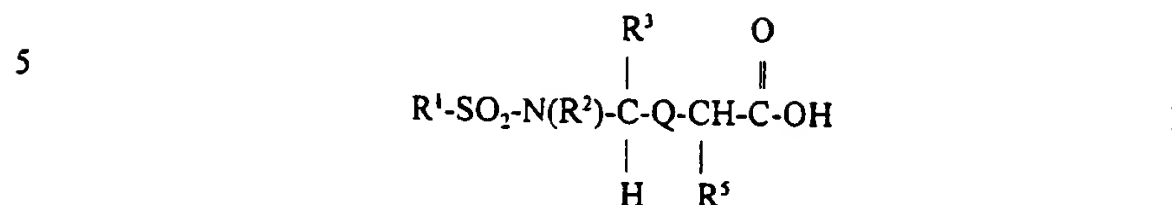
4. Q.S. to 10.0 mL with 0.5% sodium bicarbonate / saline stock solution and mix thoroughly.

5

Using a conventional oral formulation, compounds of this invention would be active in this model.

WHAT IS CLAIMED IS:

1. A compound of formula I:



10 where

R¹ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl;

15 R² is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, and R¹ and R² together with the nitrogen atom bound to R² and the SO₂ group bound to R¹ can form a heterocyclic or a substituted heterocyclic group;

20 R³ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and R² and R³ together with the nitrogen atom bound to R² and the carbon atom bound to R³ can form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted, the substituent on said saturated substituted heterocyclic group is not carboxyl;

25

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl;

x is an integer of from 1 to 4;

30 Q is -C(X)NR⁷- wherein R⁷ is selected from the group consisting of hydrogen and alkyl;

X is selected from the group consisting of oxygen and sulfur;

R^5 is $-CH_2X$ where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic,

with the further provisos that:

A. R^5 is not selected from the group consisting of $-(CH_2)_n$ -aryl and $-(CH_2)_n$ -heteroaryl where n is an integer equal to 1 to 4 when R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a saturated heterocyclic group or a saturated substituted heterocyclic group;

B. R^5 is not $-(CH_2)_x$ -Ar- $R^{5'}$ where $R^{5'}$ is $-O-Z-NR^8R^{8'}$ or $-O-Z-R^{12}$ wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycles and substituted heterocycles, and Z is selected from the group consisting of $-C(O)-$ and $-SO_2-$,

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

C. R^5 is not $-(CH_2)_x$ -Ar- $R^{5'}$ where $R^{5'}$ is selected from the group consisting of $-NR^{24}C(Z')NR^8R^{8'}$ and $-NR^{24}C(Z')R^{13}$ wherein Z' is selected from the group consisting of oxygen, sulfur and NR^{24} , R^{24} is selected from the group consisting of hydrogen, alkyl and aryl, R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,

heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl provided that when Z' is oxygen, at least one of R⁸ and R^{8'} is substituted alkyl, cycloalkyl, substituted cycloalkyl, saturated heterocyclic other than morpholino and thiomorpholino, substituted heterocyclic or R⁸ and R^{8'} can
5 be joined to form a saturated heterocycle other than morpholino or thiomorpholino, a saturated substituted heterocycle or a saturated/unsaturated heterocycle having an amino group substituted with an alkoxycarbonyl substituent, and further provided that when Z' is sulfur, at least one of R⁸ and R^{8'} is a group other than aryl, substituted aryl, heteroaryl or substituted
10 heteroaryl, R¹³ is selected from the group consisting of substituted heterocycles and saturated heterocycles other than morpholino and thiomorpholino,

Ar is aryl, substituted aryl, heteroaryl or substituted heteroaryl,
x is an integer of from 1 to 4;

15 D. R⁵ is not -ALK-X where ALK is an alkyl group of from 1 to 10 carbon atoms attached via a methylene group (-CH₂-) to the carbon atom to which it is attached; X is selected from the group consisting of substituted alkylcarbonylamino, substituted alkenylcarbonylamino, substituted alkynylcarbonylamino, heterocyclylcarbonylamino, substituted
20 heterocyclylcarbonylamino, acyl, acyloxy, aminocarbonyloxy, acylamino, oxycarbonylamino, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxy carbonyl, substituted aryloxy carbonyl, cycloalkoxy carbonyl, substituted cycloalkoxy carbonyl, heteroaryloxy carbonyl, substituted heteroaryloxy carbonyl, heterocyclyloxy carbonyl, substituted
25 heterocyclyloxy carbonyl, cycloalkyl, substituted cycloalkyl, saturated heterocyclic, substituted saturated heterocyclic, substituted alkoxy, substituted alkenoxy, substituted alkynoxy, heterocyclyloxy, substituted heterocycloxy, substituted thioalkyl, substituted thioalkenyl, substituted thioalkynyl, aminocarbonylamino, aminothi carbonylamino, guanidino,
30 amidino, alkylamidino, thioamidino, halogen, cyano, nitro, -OS(O)₂-alkyl,

-OS(O)₂-substituted alkyl, -OS(O)₂-cycloalkyl, -OS(O)₂-substituted
 cycloalkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl,
 -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted
 heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl,
 5 -NRS(O)₂-cycloalkyl, -NRS(O)₂-substituted cycloalkyl, -NRS(O)₂-aryl,
 -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted
 heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic,
 -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-
 cycloalkyl, -NRS(O)₂-NR-substituted cycloalkyl, -NRS(O)₂-NR-aryl,
 10 -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-
 substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted
 heterocyclic where R is hydrogen or alkyl, -S(O)₂-alkyl, -S(O)₂-substituted
 alkyl, -S(O)₂-aryl, -S(O)₂-substituted aryl, -S(O)₂-substituted heteroaryl, -
 S(O)₂-substituted heteroaryl, -S(O)₂-heterocyclic, -S(O)₂-substituted
 15 heterocyclic, mono- and di-(substituted alkyl)amino, N,N-(alkyl, substituted
 alkyl)amino, N,N-(aryl, substituted alkyl)amino, N,N-(substituted aryl,
 substituted alkyl)amino, N,N-(heteroaryl, substituted alkyl)amino, N,N-
 (substituted heteroaryl, substituted alkyl)amino, N,N-(heterocyclic,
 substituted alkyl)amino, N,N-N,N-(substituted heterocyclic, substituted
 20 alkyl)amino, mono- and di-(heterocyclic)amino, mono- and di-(substituted
 heterocyclic)amino, N,N-(alkyl, heterocyclic)amino, N,N-(alkyl, substituted
 heterocyclic)amino, N,N-(aryl, heterocyclic)amino, N,N-(substituted aryl,
 heterocyclic)amino, N,N-(aryl, substituted heterocyclic)amino, N,N-
 (substituted aryl, substituted heterocyclic)amino, N,N-(heteroaryl,
 25 heterocyclic)amino, N,N-(heteroaryl, substituted heterocyclic)amino, N,N-
 (substituted heteroaryl, heterocyclic)amino, N,N-(substituted heteroaryl and
 substituted heterocyclic)amino; and

E. R⁵ is not -(CH₂)_x-Ar-R^{5'} where R^{5'} is a substituent selected
 from the group consisting of:

- (a) substituted alkylcarbonylamino with the proviso that at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-\text{OS}(\text{O})_2\text{-alkyl}$, $-\text{OS}(\text{O})_2\text{-substituted alkyl}$, $-\text{OS}(\text{O})_2\text{-aryl}$, $-\text{OS}(\text{O})_2\text{-substituted aryl}$, $-\text{OS}(\text{O})_2\text{-heteroaryl}$, $-\text{OS}(\text{O})_2\text{-substituted heteroaryl}$, $-\text{OS}(\text{O})_2\text{-heterocyclic}$, $-\text{OS}(\text{O})_2\text{-substituted heterocyclic}$, $-\text{OSO}_2\text{-NRR}$, $-\text{NRS}(\text{O})_2\text{-alkyl}$, $-\text{NRS}(\text{O})_2\text{-substituted alkyl}$, $-\text{NRS}(\text{O})_2\text{-aryl}$, $-\text{NRS}(\text{O})_2\text{-substituted aryl}$, $-\text{NRS}(\text{O})_2\text{-heteroaryl}$, $-\text{NRS}(\text{O})_2\text{-substituted heteroaryl}$, $-\text{NRS}(\text{O})_2\text{-heterocyclic}$, $-\text{NRS}(\text{O})_2\text{-substituted heterocyclic}$, $-\text{NRS}(\text{O})_2\text{-NR-alkyl}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted alkyl}$, $-\text{NRS}(\text{O})_2\text{-NR-aryl}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted aryl}$, $-\text{NRS}(\text{O})_2\text{-NR-heteroaryl}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted heteroaryl}$, $-\text{NRS}(\text{O})_2\text{-NR-heterocyclic}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted heterocyclic}$, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted

- amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups and
- 5 alkyl/substituted alkyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl;
- 10 (b) alkoxyaryl substituted on the alkoxy moiety with a substituent selected from the group consisting of carboxyl and -COOR²³ where R²³ is alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl or heterocyclic;
- (c) aryl and heteroaryl;
- (d) -NR'R' wherein each R' is independently selected from the group
- 15 consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclic and substituted heterocyclic with the proviso that at least one of R' is substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic and substituted heterocyclic and with the further proviso that when R' is substituted alkyl at
- 20 least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen,
- 25 hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl,
- 30 substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl,

substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl,
thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted
heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy,
substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy,
5 oxycarbonylamino, oxythiocarbonylamino, $-\text{OS}(\text{O})_2\text{-alkyl}$, $-\text{OS}(\text{O})_2\text{-}$
substituted alkyl, $-\text{OS}(\text{O})_2\text{-aryl}$, $-\text{OS}(\text{O})_2\text{-substituted aryl}$, $-\text{OS}(\text{O})_2\text{-heteroaryl}$,
 $-\text{OS}(\text{O})_2\text{-substituted heteroaryl}$, $-\text{OS}(\text{O})_2\text{-heterocyclic}$, $-\text{OS}(\text{O})_2\text{-substituted}$
heterocyclic, $-\text{OSO}_2\text{-NRR}$, $-\text{NRS}(\text{O})_2\text{-alkyl}$, $-\text{NRS}(\text{O})_2\text{-substituted alkyl}$, $-\text{NRS}(\text{O})_2\text{-aryl}$, $-\text{NRS}(\text{O})_2\text{-substituted aryl}$, $-\text{NRS}(\text{O})_2\text{-heteroaryl}$, $-\text{NRS}(\text{O})_2\text{-}$
10 substituted heteroaryl, $-\text{NRS}(\text{O})_2\text{-heterocyclic}$,
 $-\text{NRS}(\text{O})_2\text{-substituted heterocyclic}$, $-\text{NRS}(\text{O})_2\text{-NR-alkyl}$, $-\text{NRS}(\text{O})_2\text{-NR-}$
substituted alkyl, $-\text{NRS}(\text{O})_2\text{-NR-aryl}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted aryl}$,
 $-\text{NRS}(\text{O})_2\text{-NR-heteroaryl}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted heteroaryl}$, $-\text{NRS}(\text{O})_2\text{-NR-heterocyclic}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted heterocyclic}$, mono- and di-
15 alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino,
mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono-
and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino,
mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted
amincs having different substituents selected from the group consisting of
20 alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted
heteroaryl, heterocyclic and substituted heterocyclic, substituted alkyl groups
having amino groups blocked by conventional blocking groups and
alkyl/substituted alkyl groups substituted with $-\text{SO}_2\text{-alkyl}$, $-\text{SO}_2\text{-substituted}$
alkyl, $-\text{SO}_2\text{-alkenyl}$, $-\text{SO}_2\text{-substituted alkenyl}$, $-\text{SO}_2\text{-cycloalkyl}$, $-\text{SO}_2\text{-}$
25 substituted cycloalkyl, $-\text{SO}_2\text{-aryl}$, $-\text{SO}_2\text{-substituted aryl}$, $-\text{SO}_2\text{-heteroaryl}$,
 $-\text{SO}_2\text{-substituted heteroaryl}$, $-\text{SO}_2\text{-heterocyclic}$, $-\text{SO}_2\text{-substituted heterocyclic}$
or $-\text{SO}_2\text{NRR}$, where R is hydrogen or alkyl;

(e) $-\text{alkoxy-NR}^n\text{R}^m$ wherein each R^n is independently selected from
the group consisting of alkyl, substituted alkyl, aryl, substituted aryl,
30 cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl,

heterocyclic, and substituted heterocyclic with the proviso that when each R¹ is substituted alkyl then at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted

- amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups and
- 5 alkyl/substituted alkyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl;
- 10 (f) substituted alkenyl or substituted alkynyl with the proviso that at least one of the substituents on the substituted alkenyl/alkynyl moiety is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic with the proviso that
- 15 when substituted with substituted alkyl then at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocabonylamino, aminocarbonyloxy, aryloxy,
- 20 substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone,
- 25 thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy,
- heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -
- 30

OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, and substituted alkyl groups having amino groups blocked by conventional blocking groups, and alkyl/substituted alkyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl;

(g) substituted aryloxy and substituted heteroaryloxy with the proviso that at least one substituent on the substituted aryloxy/heteroaryloxy is other than halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

- (h) -alkoxy-saturated heterocyclic, -alkoxy-saturated substituted heterocyclic, -substituted alkoxy-heterocyclic and -substituted alkoxy-substituted saturated heterocyclic;
- (i) -O-heterocyclic and -O-substituted heterocyclic;
- 5 (j) tetrazolyl;
- (k) -NR-SO₂-substituted alkyl where R is hydrogen, alkyl or aryl, with the proviso that at least one substituent on the alkyl moiety of the substituted alkylsulfonylamino is other than halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl,
- 10 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;
- (l) alkenylsulfonylamino, alkynylsulfonylamino, substituted
- 15 alkenylsulfonylamino and substituted alkynylsulfonylamino;
- (m) substituted alkoxy with the proviso that the substitution on the alkyl moiety of said substituted alkoxy does not include alkoxy-NR"R", as defined above, unsaturated heterocyclyl, alkyloxy, aryloxy, heteroaryloxy, aryl, heteroaryl and aryl/heteroaryl substituted with halogen, hydroxyl,
- 20 amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;
- 25 (n) amidine and amidine substituted with from 1 to 3 substituents independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic;
- (o) -C(O)NR""R"" where each R"" is independently selected from the
- 30 group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted

cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when one R^{'''} is unsaturated heterocyclic, aryl, heteroaryl or aryl/heteroaryl substituted with halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea, then the other R^{'''} is alkyl, substituted alkyl (other than unsaturated heterocyclyl substituted-alkyl), cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heterocyclic or substituted heterocyclic;

(p) -NR²²C(O)-R¹⁸ where R¹⁸ is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, and R²² is alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

(q) -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl or -SO₂-alkyl;

(r) -NR'C(O)NR¹⁹R¹⁹ wherein R' is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and each R¹⁹ is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic:

(s) -NR'C(O)OR¹⁹ wherein R' is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted

heterocyclic, and R¹⁹ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

5 (t) -aminocarbonyl-(N-formylheterocyclyl); and

(u) -alkyl-C(O)NH-heterocyclyl and -alkyl-C(O)NH-substituted heterocyclyl,

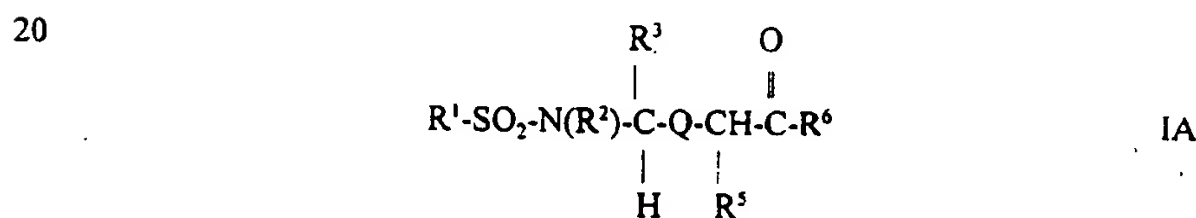
and pharmaceutically acceptable salts thereof;

10 and still further with the following provisos excluding the following compounds:

A. when R¹ is *p*-methylphenyl, R² and R³ together with their pendent nitrogen and carbon atoms form a pyrrolidinyl ring and Q is -C(O)NH-, then R⁵ is not -CH₂COOH or -CH₂CH₂COOH; and

15 B. when R¹ is *p*-methylphenyl, R² and R³ together with their pendent nitrogen and carbon atoms form a pyrrolidinyl ring and Q is -C(O)NH-, then R⁵ is not 2,4,6-trimethylbenzyl.

2. A compound of the formula:



25 where

R¹ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl;

30 R² is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl,

heteroaryl, substituted heteroaryl, and R^1 and R^2 together with the nitrogen atom bound to R^2 and the SO_2 group bound to R^1 can form a heterocyclic or a substituted heterocyclic group;

R^3 is selected from the group consisting of hydrogen, alkyl,
 5 substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 can form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted,
 10 the substituent on said saturated substituted heterocyclic group is not carboxyl;

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl;

x is an integer of from 1 to 4;

R^6 is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-
 15 3-yl (3,4-enol), amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3- β -yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl, -NH(CH₂)_pCOOY where p is an integer of from 1 to 8 and Y is as defined above, -OCH₂NR⁹R¹⁰ where R⁹ is selected from the group consisting
 20 of -C(O)-aryl and -C(O)-substituted aryl and R¹⁰ is selected from the group consisting of hydrogen and -CH₂COOR¹¹ where R¹¹ is alkyl, and -NHSO₂Z" where Z" is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

25 Q is -C(X)NR⁷- wherein R⁷ is selected from the group consisting of hydrogen and alkyl;

X is selected from the group consisting of oxygen and sulfur;

R⁸ is -CH₂X where X is selected from the group consisting of
 hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl,
 30 carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl,

carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl,
 carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic,
 carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted
 alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl,
 5 substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and
 substituted heterocyclic;

with the further provisos that:

A. R^5 is not selected from the group consisting of $-(CH_2)_n$ -aryl
 and $-(CH_2)_n$ -heteroaryl where n is an integer equal to 1 to 4 when R^2 and R^3
 10 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3
 form a saturated heterocyclic group or a saturated substituted heterocyclic
 group;

B. R^5 is not $-(CH_2)_x$ -Ar- $R^{5'}$ where $R^{5'}$ is $-O-Z-NR^8R^{8'}$ or $-O-Z-R^{12}$
 wherein R^8 and $R^{8'}$ are independently selected from the group consisting of
 15 hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl,
 heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to
 form a heterocycle or a substituted heterocycle, R^{12} is selected from the
 group consisting of heterocycles and substituted heterocycles, and Z is
 selected from the group consisting of $-C(O)-$ and $-SO_2-$,

20 Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,
 x is an integer of from 1 to 4;

C. R^5 is not $-(CH_2)_x$ -Ar- $R^{5'}$ where $R^{5'}$ is selected from the group
 consisting of $-NR^{24}C(Z')NR^8R^{8'}$ and $-NR^{24}C(Z')R^{13}$ wherein Z' is selected
 from the group consisting of oxygen, sulfur and NR^{24} , R^{24} is selected from
 25 the group consisting of hydrogen, alkyl and aryl, R^8 and $R^{8'}$ are
 independently selected from the group consisting of hydrogen, alkyl,
 substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,
 heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl
 provided that when Z' is oxygen, at least one of R^8 and $R^{8'}$ is substituted alkyl,
 30 cycloalkyl, substituted cycloalkyl, saturated heterocyclic other than

- morpholino and thiomorpholino, substituted heterocyclic or R^8 and R^8 can be joined to form a saturated heterocycle other than morpholino or thiomorpholino, a saturated substituted heterocycle or a saturated/unsaturated heterocycle having an amino group substituted with an alkoxycarbonyl substituent, and further provided that when Z' is sulfur, at least one of R^8 and R^8 is a group other than aryl, substituted aryl, heteroaryl or substituted heteroaryl, R^{13} is selected from the group consisting of substituted heterocycles and saturated heterocycles other than morpholino and thiomorpholino,
- 10 Ar is aryl, substituted aryl, heteroaryl or substituted heteroaryl, x is an integer of from 1 to 4;
- D. R^5 is not -ALK-X where ALK is an alkyl group of from 1 to 10 carbon atoms attached via a methylene group (-CH₂-) to the carbon atom to which it is attached; X is selected from the group consisting of substituted
- 15 alkylcarbonylamino, substituted alkenylcarbonylamino, substituted alkynylcarbonylamino, heterocyclylcarbonylamino, substituted heterocyclylcarbonylamino, acyl, acyloxy, aminocarbonyloxy, acylamino, oxycarbonylamino, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxy carbonyl, substituted aryloxy carbonyl, cycloalkoxycarbonyl,
- 20 substituted cycloalkoxycarbonyl, heteroaryloxy carbonyl, substituted heteroaryloxy carbonyl, heterocyclyloxy carbonyl, substituted heterocyclyloxy carbonyl, cycloalkyl, substituted cycloalkyl, saturated heterocyclic, substituted saturated heterocyclic, substituted alkoxy, substituted alkenoxy, substituted alkynoxy, heterocyclyloxy, substituted
- 25 heterocycloxy, substituted thioalkyl, substituted thioalkenyl, substituted thioalkynyl, aminocarbonylamino, aminothiocabonylamino, guanidino, amidino, alkylamidino, thioamidino, halogen, cyano, nitro, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-cycloalkyl, -OS(O)₂-substituted cycloalkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl,

-OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted
 heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl,
 -NRS(O)₂-cycloalkyl, -NRS(O)₂-substituted cycloalkyl, -NRS(O)₂-aryl,
 -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted
 5 heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic,
 -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-
 cycloalkyl, -NRS(O)₂-NR-substituted cycloalkyl, -NRS(O)₂-NR-aryl,
 -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-
 substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted
 10 heterocyclic, -S(O)₂-alkyl, -S(O)₂-substituted alkyl, -S(O)₂-aryl,
 -S(O)₂-substituted aryl, -S(O)₂-substituted heteroaryl, -S(O)₂-substituted
 heteroaryl, -S(O)₂-heterocyclic, -S(O)₂-substituted heterocyclic, mono- and
 di-(substituted alkyl)amino, N,N-(alkyl, substituted alkyl)amino, N,N-(aryl,
 substituted alkyl)amino, N,N-(substituted aryl, substituted alkyl)amino, N,N-
 15 (heteroaryl, substituted alkyl)amino, N,N-(substituted heteroaryl, substituted
 alkyl)amino, N,N-(heterocyclic, substituted alkyl)amino, N,N-N,N-
 (substituted heterocyclic, substituted alkyl)amino, mono- and di-
 (heterocyclic)amino, mono- and di-(substituted heterocyclic)amino, N,N-
 (alkyl, heterocyclic)amino, N,N-(alkyl, substituted heterocyclic)amino, N,N-
 20 (aryl, heterocyclic)amino, N,N-(substituted aryl, heterocyclic)amino, N,N-
 (aryl, substituted heterocyclic)amino, N,N-(substituted aryl, substituted
 heterocyclic)amino, N,N-(heteroaryl, heterocyclic)amino, N,N-(heteroaryl,
 substituted heterocyclic)amino, N,N-(substituted heteroaryl,
 heterocyclic)amino, N,N-(substituted heteroaryl and substituted
 25 heterocyclic)amino; and

E. R⁵ is not -(CH₂)_x-Ar-R^{5'} where R^{5'} is a substituent selected from the group consisting of:

(a) substituted alkylcarbonylamino with the proviso that at least one
 of the substituents on the substituted alkyl moiety is selected from the group
 30 consisting of alkoxy, substituted alkoxy, acyl, acylamino,

thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino,
 thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino,
 aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen,
 hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-
 5 cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-
 substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl,
 carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl,
 substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl,
 substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl,
 10 substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl,
 thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted
 heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy,
 substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy,
 oxycarbonylamino, oxythiocarbonylamino, $-\text{OS}(\text{O})_2\text{-alkyl}$, $-\text{OS}(\text{O})_2\text{-}$
 15 substituted alkyl, $-\text{OS}(\text{O})_2\text{-aryl}$, $-\text{OS}(\text{O})_2\text{-substituted aryl}$, $-\text{OS}(\text{O})_2\text{-heteroaryl}$,
 $-\text{OS}(\text{O})_2\text{-substituted heteroaryl}$, $-\text{OS}(\text{O})_2\text{-heterocyclic}$, $-\text{OS}(\text{O})_2\text{-substituted}$
 heterocyclic, $-\text{OSO}_2\text{-NRR}$, $-\text{NRS}(\text{O})_2\text{-alkyl}$, $-\text{NRS}(\text{O})_2\text{-substituted alkyl}$,
 $-\text{NRS}(\text{O})_2\text{-aryl}$, $-\text{NRS}(\text{O})_2\text{-substituted aryl}$, $-\text{NRS}(\text{O})_2\text{-heteroaryl}$, $-\text{NRS}(\text{O})_2\text{-}$
 substituted heteroaryl, $-\text{NRS}(\text{O})_2\text{-heterocyclic}$, $-\text{NRS}(\text{O})_2\text{-substituted}$
 20 heterocyclic, $-\text{NRS}(\text{O})_2\text{-NR-alkyl}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted alkyl}$, $-\text{NRS}(\text{O})_2\text{-NR-aryl}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted aryl}$,
 $-\text{NRS}(\text{O})_2\text{-NR-heteroaryl}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted heteroaryl}$, $-\text{NRS}(\text{O})_2\text{-NR-heterocyclic}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted heterocyclic}$, mono- and di-
 alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino,
 25 mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono-
 and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino,
 mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted
 amines having different substituents selected from the group consisting of
 alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted
 30 heteroaryl, heterocyclic, and substituted heterocyclic, substituted alkyl

groups having amino groups blocked by conventional blocking groups and alkyl/substituted alkyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl;

(b) alkoxyaryl substituted on the alkoxy moiety with a substituent selected from the group consisting of carboxyl and -COOR²³ where R²³ is alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl or heterocyclic;

(c) aryl and heteroaryl;

(d) -NR'R' wherein each R' is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclic and substituted heterocyclic with the proviso that at least one of R' is substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic and substituted heterocyclic and with the further proviso that when R' is substituted alkyl at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy,

- substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups and alkyl/substituted alkyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl;
- (e) -alkoxy-NR''R'' wherein each R'' is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic with the proviso that when each R'' is substituted alkyl then at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted

alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-

5 substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl,

10 thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -

15 OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-

20 substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-

25 (substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,

30

heterocyclic and substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups and alkyl/substituted alkyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl,
5 -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic or -SO₂NRR, where R is hydrogen or alkyl;

(f) substituted alkenyl or substituted alkynyl with the proviso that at least one of the substituents on the substituted alkenyl/alkynyl moiety is
10 selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic with the proviso that when substituted with substituted alkyl then at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of
15 alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted
20 cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted
25 thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-

substituted heterocyclic, -OSO₂-NRR, -NRS(O)₂-alkyl, -NRS(O)₂-substituted
 alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -
 NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-
 substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted
 5 alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-
 heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic,
 -NRS(O)₂-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and
 di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-
 (substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-
 10 (substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and
 di-(substituted heterocyclic) amino, unsymmetric di-substituted amines
 having different substituents selected from the group consisting of alkyl,
 substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,
 heterocyclic and substituted heterocyclic, and substituted alkyl groups having
 15 amino groups blocked by conventional blocking groups and alkyl/substituted
 alkyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-
 alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted
 cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, SO₂-substituted
 heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic or -SO₂NRR,
 20 where R is hydrogen or alkyl;

(g) substituted aryloxy and substituted heteroaryloxy with the proviso
 that at least one substituent on the substituted aryloxy/heteroaryloxy is other
 than halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy,
 alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy,
 25 alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino,
 alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino,
 alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(h) -alkoxy-saturated heterocyclic, -alkoxy-saturated substituted
 heterocyclic, -substituted alkoxy-heterocyclic and -substituted alkoxy-
 30 substituted saturated heterocyclic;

(i) -O-heterocyclic and -O-substituted heterocyclic;

(j) tetrazolyl;

(k) -NR-SO₂-substituted alkyl where R is hydrogen, alkyl or aryl,
with the proviso that at least one substituent on the alkyl moiety of the
5 substituted alkylsulfonylamino is other than halogen, hydroxyl, amino, nitro,
trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-
dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy,
alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl,
alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or
10 N,N-dialkylurea;

(l) alkenylsulfonylamino, alkynylsulfonylamino, substituted
alkenylsulfonylamino and substituted alkynylsulfonylamino;

(m) substituted alkoxy with the proviso that the substitution on the
alkyl moiety of said substituted alkoxy does not include alkoxy-NR''R'', as
15 defined above, unsaturated heterocyclyl, alkyloxy, aryloxy, heteroaryloxy,
aryl, heteroaryl and aryl/heteroaryl substituted with halogen, hydroxyl,
amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-
dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy,
alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl,
20 alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or
N,N-dialkylurea;

(n) amidine and amidine substituted with from 1 to 3 substituents
independently selected from the consisting of alkyl, substituted alkyl,
alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and
25 heterocyclic;

(o) -C(O)NR'''R''' where each R''' is independently selected from the
group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted
cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl,
substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and
30 substituted heterocyclic with the proviso that when one R''' is unsaturated

heterocyclic, aryl, heteroaryl or aryl/heteroaryl substituted with halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea, then the other R''' is alkyl, substituted alkyl (other than unsaturated heterocyclyl substituted-alkyl), cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heterocyclic or substituted heterocyclic;

10 (p) $-NR^{22}C(O)-R^{18}$ where R^{18} is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, and R^{22} is alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

15 (q) $-SO_2$ -aryl, $-SO_2$ -substituted aryl, $-SO_2$ -heteroaryl, $-SO_2$ -substituted heteroaryl or $-SO_2$ -alkyl;

(r) $-NR'C(O)NR^{19}R^{19}$ wherein R' is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and each R^{19} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

25 (s) $-NR'C(O)OR^{19}$ wherein R' is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, and R^{19} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted

aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

(t) -aminocarbonyl-(N-formylheterocyclyl); and

(u) -alkyl-C(O)NH-heterocyclyl and -alkyl-C(O)NH-substituted
5 heterocyclyl,

and pharmaceutically acceptable salts thereof;

with the following provisos:

A) when R¹ is *p*-methylphenyl, R² and R³ together with their pendent nitrogen and carbon atoms form a pyrrolidinyl ring, R⁵ is
10 *p*-[-OCH₂CH₂-(4,5-dihydroimidazol-2-yl), Q is -C(O)NH-, then R⁶ is not -O-methyl;

B) when R¹ is 4-fluorobenzyl, R²/R³ together equal L-pyrrolidinyl, and R⁵ is 4-hydroxybenzyl, then R⁶ is not isopropyl;

C) when R¹ is 1-methylimidazole, R²/R³ together equal L-
15 pyrrolidinyl, and R⁵ is 4-hydroxybenzyl, then R⁶ is not *t*-butyl; and

D) when R¹ is 4-trifluoromethoxybenzyl, R²/R³ together equal 5,5-dimethylthiazolidin-4-yl, and R⁵ is 4-hydroxybenzyl, then R⁶ is not *t*-butyl.

3. A compound of Claims 1 or 2 wherein R¹ is selected from the
20 group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl.

4. A compound of Claims 1 or 2 wherein R¹ is selected from the
group consisting of 4-methylphenyl, methyl, benzyl, *n*-butyl, 4-chlorophenyl,
25 1-naphthyl, 2-naphthyl, 4-methoxyphenyl, phenyl, 2,4,6-trimethylphenyl, 2-(methoxycarbonyl)phenyl, 2-carboxyphenyl, 3,5-dichlorophenyl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl, 3,4-dimethoxyphenyl, 4-(CH₃C(O)NH-)phenyl, 4-trifluoromethoxyphenyl, 4-cyanophenyl, isopropyl, 3,5-di-(trifluoromethyl)phenyl, 4-*t*-butylphenyl, 4-*t*-butoxyphenyl, 4-
30 nitrophenyl, 2-thienyl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl,

phenethyl, 1-N-methylimidazol-4-yl, 4-bromophenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-[CH₃SC(=NH)]phenyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methyl-4-pyrazolyl, 2-thiazolyl, 5-methyl-1,3,4-thiadiazol-2-yl, 4-[H₂NC(S)]phenyl, 4-aminophenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,5-difluorophenyl, pyridin-3-yl, pyrimidin-2-yl, 4-(3'-dimethylamino-*n*-propoxy)-phenyl, and 1-methylpyrazol-4-yl.

5. A compound of Claims 1 or 2 wherein R² is selected from the group consisting of hydrogen, methyl, phenyl, benzyl, -(CH₂)₂-2-thienyl, and -(CH₂)₂- ϕ .

6. A compound of Claims 1 or 2 wherein R¹ and R² together with the nitrogen atom bound to R² and the SO₂ group bound to R¹ are joined to form a heterocyclic group or substituted heterocyclic group.

7. A compound of Claims 1 or 2 wherein R³ includes all of the isomers arising by substitution with methyl, phenyl, benzyl, diphenylmethyl, -CH₂CH₂-COOH, -CH₂-COOH, 2-amidoethyl, *iso*-butyl, *t*-butyl, -CH₂O-benzyl and hydroxymethyl.

8. A compound of Claims 1 or 2 wherein R² and R³ together with the nitrogen atom bound to R² and the carbon atom bound to R³ form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted, the substituent on said saturated substituted heterocyclic group is not carboxyl.

9. A compound of Claims 1 or 2 wherein Q is -C(O)NH- or -C(S)NH-.

10. A compound of Claims 1 or 2 wherein R⁵ is selected from the group consisting of *p*-[-OCH(CH₃)φ]benzyl, 4-hydroxybenzyl, 2-carboxybenzyl, 3-carboxybenzyl, 4-carboxybenzyl, 4-(2-carboxyphenoxy)benzyl, 4-(benzyloxy)benzyl, 4-iodobenzyl, 4-methoxybenzyl, 4-nitrobenzyl, 4-(*tert*-butoxy)benzyl, 3,5-diiodo-4-hydroxybenzyl, 4-(benzamido)benzyl, benzyl, 4-hydroxy-3-iodobenzyl, 4-chlorobenzyl, isobutyl, methyl, 4-(acetamido)benzyl, *n*-butyl, carboxymethyl, 4-aminobutyl, 2-carboxyethyl, 4-(*N,N*-dibenzylamino)benzyl, (*N*-benzylimidazol-4-yl)methyl, 2-thiomethoxyethyl, hydroxymethyl, (*N*-methylimidazol-4-yl)methyl, 4-(isopropyl-C(O)NH-)butyl, 4-(benzamido)butyl, 4-(benzyl-C(O)NH-)butyl, (*N*-methylimidazol-5-yl)methyl, 4-(pyridin-2-yl-C(O)NH-)butyl, 4-(6-methylpyridin-3-yl-C(O)NH-)butyl, 4-(3-methylthien-2-yl-C(O)NH-)butyl, 4-(pyrrol-2-yl-C(O)NH-)butyl, 4-(furan-2-yl-C(O)NH-)butyl, isopropyl, 4-aminobenzyl, 4-(4-phenylbutoxy)benzyl, 4-(1-methylindol-3-yl-C(O)NH-)butyl, 4-(4-methanesulfonylphenyl-C(O)NH-)butyl, 4-(4-acetylphenyl-C(O)NH-)butyl, 4-(4-fluorophenyl-C(O)NH-)butyl, 4-[2-(pyridin-2-yl)ethynyl]benzyl, 4-[2-(3-hydroxyphenyl)ethynyl]benzyl, 4-(pyridin-4-yl-C(O)NH-)benzyl, 4-(pyridin-3-yl-C(O)NH-)benzyl, 4-(3-methylphenyl-NHC(O)NH-)benzyl, 4-(2,3-dihydroindol-2-yl-C(O)NH-)benzyl, 4-(*N,N*-dipentylamino)benzyl, 4-(*N*-pentylamino)benzyl, 4-[2-(*N,N*-dibenzylamino)ethoxy]benzyl, 3-hydroxybenzyl, 4-(*N-n*-butyl-*N-n*-pentylamino)benzyl, 4-(*N*-4-chlorophenylamino)benzyl, 4-(4-cyanophenyl-NHC(O)NH-)benzyl, 4-(carboxymethoxy)benzyl, 4-(*tert*-butoxycarbonylmethoxy)benzyl, 4-(5-fluoroindol-2-yl-C(O)NH-)benzyl, 4-(1,2,3,4-tetrahydroisoquinolin-3-yl-C(O)NH-)benzyl, 4-(3-methoxyphenyl-NHC(O)NH-)benzyl, 4-[2-(indol-3-yl)ethoxy]benzyl, 4-(4,5-dihydroimidazol-2-ylmethoxy)benzyl, 4-(*n*-propyl-NHC(O)NH-)benzyl, 4-(*N*-benzylamino)benzyl, 3-methoxybenzyl, 4-(pyridin-2-yl-C(O)NH-)benzyl, 4-(*N*-4-chlorobenzylamino)benzyl, 4-(2-chloromethylsulfonylamino)benzyl, 4-(*N,N*-dimethylamino)benzyl, 3-

aminobenzyl, 4-(benzyl)benzyl, 2-hydroxyethyl, 4-nitrobenzyl, 4-(phenyl-
 NHC(S)NH-)benzyl, 4-(pyridin-3-yl-NHC(S)NH-)benzyl, 4-(pyridin-4-
 ylmethylamino)benzyl, 4-[ϕ CH₂OCH₂(Boc-HN)CHC(O)NH-]benzyl, 4-
 (pyridin-3-yl-C(O)NH-)butyl, 4-(pyridin-4-yl-C(O)NH-)butyl, 4-(pyridin-3-
 5 yl-C(O)NH-)benzyl, 4-(pyridin-4-yl-C(O)NH-)benzyl, 4-(*N*-
 toluenesulfonylpyrrolidin-2-yl-C(O)NH-)butyl, 4-(piperidin-4-yl-C(O)NH-
)butyl, 4-(2-Boc-1,2,3,4-tetrahydroisoquinolin-3-yl-NHCH₂-)benzyl, 4-(2-
 Boc-1,2,3,4-tetrahydroisoquinolin-3-yl-C(O)NH-)benzyl, 4-(pyridin-3-
 ylmethylamino)benzyl, 4-[ϕ CH₂O(O)C(CbzNH)CHCH₂CH₂C(O)NH-
 10]benzyl, 4-(2-methoxybenzamido)benzyl, 4-(2-bromobenzamido)benzyl, 4-
 (pyrazin-2-yl-C(O)NH-)benzyl, (1-toluenesulfonylimidizol-4-yl)methyl, [1-
 (*N,N*-dimethylaminosulfonyl)imidizol-4-yl]methyl, 4-
 (trifluoromethyl)benzyl, 4-(3,3-dimethylureido)benzyl, 4-
 (methoxycarbonylamino)benzyl, 4-(1,3,3-trimethylureido)benzyl, 4-
 15 (methoxycarbonyl-*N*-methylamino)benzyl, 4-cyanobenzyl, 4-(2-formyl-
 1,2,3,4-tetrahydroisoquinolin-3-yl-C(O)NH-)benzyl, phenyl, 4-
 (aminomethyl)benzyl, 4-(1-Boc-piperidin-4-yl-C(O)NHCH₂-)benzyl, 4-(1-
 Boc-piperidin-4-yl-C(O)O-)benzyl, 4-(piperidin-4-yl-C(O)NHCH₂-)benzyl,
 4-[(1-methylpiperidin-4-yl)-O-]benzyl, 4-(1,2,3,4-tetrahydroquinolin-2-yl-
 20 C(O)NH-)benzyl, α -methylbenzyl, 4-(trimethylacetamido)benzyl, 4-(2-
 methylpropionamido)benzyl, 4-(morpholin-4-yl-C(O)NH-)benzyl, 4-(3,3-
 diethylureido)benzyl, 4-(2-trifluoromethylbenzamido)benzyl, 4-(2-
 methylbenzamido)benzyl, 4-hydroxy-3-nitrobenzyl, 3-hydroxy-4-(ϕ -
 OC(O)NH-)benzyl, 4-(thiomorpholino-4-yl-C(O)NH-)benzyl, 4-(1,1-
 25 dioxothiomorpholino-4-yl-C(O)NH-)benzyl, 3-nitro-4-
 (methoxycarbonylmethoxy)benzyl, (2-benzoxazolinon-6-yl)methyl, (2*H*-1,4-
 benzoxazin-3(4*H*)-one-7-yl)methyl, 4-[*N,N*-dimethylaminosulfonyl-(*N*-
 methyl)amino]benzyl, 4-[(2-methylpyrrolidin-1-yl)-C(O)NH-]benzyl,
 (pyridin-4-yl)methyl, 4-(1-methylpiperidin-4-yl-C(O)NH-)benzyl, 4-
 30 [bis(*N,N*-dimethylaminothiocarbonyl)amino]benzyl, 4-(*N,N*-

dimethylaminosulfonyl)benzyl, 4-(imidazolid-2-one-1-yl)benzyl, 3,4-(ethylenedioxy)benzyl-, 3,4-(methylenedioxy)benzyl- and 4-(3-formylimidazolid-2-one-1-yl)benzyl.

- 5 11. A compound of Claim 2 wherein R⁶ is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), methoxy, ethoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, cyclopentoxy, *neo*-pentoxy, 2- α -*iso*-propyl-4- β -methylcyclohexoxy, 2- β -isopropyl-4- β -methylcyclohexoxy, -NH₂, benzyloxy, -NHCH₂COOH, -NHCH₂CH₂COOH, -NH-adamantyl, 10 -NHCH₂CH₂COOCH₂CH₃, -NHSO₂-*p*-CH₃- ϕ , -NHOR⁸ where R⁸ is hydrogen, methyl, *iso*-propyl or benzyl, O-(N-succinimidyl), -O-cholest-5-en-3- β -yl, -OCH₂-OC(O)C(CH₃)₃, -O(CH₂)_zNHC(O)W where *z* is 1 or 2 and W is selected from the group consisting of pyrid-3-yl, N-methylpyridyl, and N-methyl-1,4-dihydro-pyrid-3-yl, and -NR'¹⁵C(O)-R' where R' is aryl, heteroaryl or heterocyclic and R'' is hydrogen or -CH₂C(O)OCH₂CH₃.

12. A compound selected from the group consisting of:
- 20 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-(α -methylbenzyloxy)-L-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-tyrosine
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-carboxyphenylalanine
- 25 *N*-(Toluene-4-sulfonyl)-L-prolyl-3-(carboxy)phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-(2-carboxyphenoxy)-L-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-O-(benzyl)-L-tyrosine
- 30 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-(iodo)-L-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(methoxy)-phenylalanine
- 35 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-nitro-L-phenylalanine

- N*-(Toluene-4-sulfonyl)-L-prolyl-4-(*O*-*tert*-butyl)-L-tyrosine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(3,5-diiodo)-tyrosine
- 5 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(aminobenzoyl)-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(3-iodo-4-hydroxy)-phenylalanine
- 10 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-chloro)phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-leucine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-alanine
- 15 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(acetamido)-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-isoleucine
- 20 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-aspartic acid
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-lysine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-glutamic acid
- 25 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-dibenzylamino)-phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(*N*-benzyl)-histidine
- 30 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-dibenzylamino)-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-methionine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-serine
- 35 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-(*N*-benzyl)-histidine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(1-methyl)histidine
- 40 *N*-(Toluene-4-sulfonyl)-L-prolyl-D-(*N*-benzyl)histidine
- N*-(Toluene-4-sulfonyl)-L-glutamyl-L-tyrosine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(*N*-3-methyl)histidine

- N*-(Toluene-4-sulfonyl)-L-prolyl- α -amino-2,3-dihydro-(1,4-benzodioxin)-6-propanoic acid
- 5 *N*-(Toluene-4-sulfonyl)-L-prolyl- α -amino-1,3-benzodioxole-5-propanoic acid
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-valine
- 10 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-iodo)-phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(aminobenzoyl)phenylalanine methyl ester
- 15 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-chloro)phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-amino)phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-acetamido)phenylalanine methyl ester
- 20 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-(*N*-benzyl)-histidine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-(3-3'-tolylureido)-L-phenylalanine
- 25 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-[(2,3,3a,7a-tetrahydro-1H-indole-2-carbonyl)-amino]-L-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-pentylamino)phenylalanine methyl ester
- 30 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-*O*-(2-dibenzylamino-ethyl)-tyrosine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-*O*-[2-(dibenzylamino)ethyl]-tyrosine
- 35 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-pentylamino)phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(4-chlorobenzylamino)-phenylalanine methyl ester
- 40 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[3-(4-cyanophenyl)-ureido]-phenylalanine methyl ester

- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[3-(4-cyanophenyl)-ureido]-phenylalanine
- 5 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-*O*-(*tert*-butoxycarbonylmethyl)-tyrosine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-*O*-(*tert*-butoxycarbonylmethyl)-tyrosine
- 10 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[(3*S*)-3,4-dihydro-isoquinolin-3-yl-aminocarbonyl]-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-[3-(3-methoxy-phenyl)-ureido]-L-phenylalanine methyl ester
- 15 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-[3-(3-methoxy-phenyl)-ureido]-L-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-*O*-(4,5-dihydro-1*H*-imidazol-2-yl-methyl)-tyrosine
- 20 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(3-propyl-ureido)-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-benzylamino)phenylalanine
- 25 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-benzylamino)phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(4-chlorobenzylamino)-phenylalanine
- 30 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-chloromethanesulfonylamino)-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-(aminobenzoyl)phenylalanine methyl ester
- 35 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-(benzamido)phenylalanine
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-tyrosine ethyl ester
- 40 *N*-(Toluene-4-Sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-tyrosine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[(pyridin-4-yl)methylamino]phenylalanine

- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[(pyridin-4-yl)methylamino]phenylalanine methyl ester
- 5 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-(pyridin-3-carboxamido)phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-(pyridine-3-carboxamido)phenylalanine
- 10 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[(pyridin-3-ylmethyl)amino]phenylalanine
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-nitrophenylalanine methyl ester
- 15 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-nitrophenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-methoxybenzamido)phenylalanine ethyl ester
- 20 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-(4-nitro)phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-bromobenzamido)phenylalanine ethyl ester
- 25 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiamorphyl-L-4-aminophenylalanine ethyl ester
- 30 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-acetamidophenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-methoxybenzamido)phenylalanine
- 35 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-acetamidophenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-acetamidophenylalanine
- 40 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-acetamidophenylalanine isopropyl ester
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-L-4-(isonicotinamido)phenylalanine ethyl ester

- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(isonicotinamido)phenylalanine ethyl ester
- 5 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(π -toluene-4-sulfonyl)histidine methyl ester
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-(nicotinamido)phenylalanine ethyl ester
- 10 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(*O*-methyl)tyrosine ethyl ester
- N*-(α -Toluenesulfonyl)-L-prolyl-L-4-(isonicotinamido)phenylalanine ethyl ester
- 15 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-bromobenzamido)phenylalanine
- N*-(α -Toluenesulfonyl)-L-prolyl-L-4-(isonicotinamido)phenylalanine
- 20 *N*-(Toluene-4-sulfonyl)-L-(1,1-dioxo)thiamorpholyl-L-4-(2-bromobenzamido))phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-(1,1-dioxo)thiamorpholyl-L-4-(2-bromobenzamido)phenylalanine
- 25 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-L-4-(isonicotinamido)phenylalanine
- N*-(α -Toluenesulfonyl)-L-prolyl-L-4-(2-bromobenzamido)phenylalanine ethyl ester
- 30 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-tyrosine isopropyl ester
- 35 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-tyrosine *tert*-butyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-tyrosine *tert*-butyl ester
- 40 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-trifluoromethylbenzamido)phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-methylbenzamido)phenylalanine ethyl ester

- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-trifluoromethylbenzamido)
phenylalanine
- 5 *N*-(4-Fluorobenzenesulfonyl)-L-thiaprolyl-L-tyrosine *tert*-butyl Ester
- N*-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-tyrosine *tert*-
butyl ester
- 10 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-(dimethylamino)-L-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-[(2-bromo)benzamido]-L-phenylalanine
ethyl ester
- 15 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-[(pyrazin-2-yl)C(O)NH]-L-phenylalanine
methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-(4-nitrobenzoyl)-L-phenylalanine ethyl
ester
- 20 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-4-(2-bromobenzamido)-
L-phenylalanine *t*-butyl ester
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-4-(2-bromobenzamido)-
L-phenylalanine *t*-butyl ester
- 25 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-(1-H-2-oxo-3-
methyltetrahydropyrimidin-1-yl)-L-phenylalanine *t*-butyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-(1-H-2-oxo-3-
methyltetrahydropyrimidin-1-yl)-L-phenylalanine
- 30 *N*-(Toluene-4-sulfonyl)-L-prolyl-3-chloro-4-(*t*-butoxy)-L-phenylalanine *t*-
butyl ester
- 35 *N*-(Toluene-4-sulfonyl)-L-prolyl-3-chloro-4-(hydroxy)-L-phenylalanine *t*-
butyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-(*N,N*-dimethylureido)-L-phenylalanine *t*-
butyl ester
- 40 *N*-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-chloro-4-
(hydroxy)-L-phenylalanine *t*-butyl ester

- N-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-chloro-4-(hydroxy)-L-phenylalanine isopropyl ester
- 5 N-(Toluene-4-sulfonyl)-L-prolyl-4-(2-methoxyphenyl)-L-phenylalanine t-butyl ester
- N-(Toluene-4-sulfonyl)-L-prolyl-4-(2-methoxyphenyl)-L-phenylalanine
- 10 N-(Toluene-4-sulfonyl)-L-prolyl-[(5-N,N-dimethyl ureido)-pyridin-2-yl]-alanine
- N-(Toluene-4-sulfonyl)-L-prolyl-4-(N,N-dimethylsulfamyl)-L-phenylalanine
- 15 N-(Toluene-4-sulfonyl)-L-prolyl-4-(N¹,N¹,N²-trimethylsulfamyl)-L-phenylalanine
- N-(Toluene-4-sulfonyl)-L-prolyl-(1-t-butoxycarbonylmethylimidazol-4-yl)-L-alanine methyl ester
- 20 N-(Toluene-4-sulfonyl)-L-prolyl-[N,N-dimethylaminocarbonylmethylimidazol-4-yl]-L-alanine methyl ester
- N-[4-(dimethyl ureylenyl)-benzenesulfonyl]-L-prolyl-4-hydroxy-L-phenylalanine isopropyl ester
- 25 N-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-chloro-4-hydroxy-L-phenylalanine isopropyl ester
- N-(Toluene-4-sulfonyl)-L-prolyl-3-chloro-4-hydroxy-L-phenylalanine isopropyl ester
- 30 N-(Toluene-4-sulfonyl)-L-prolyl-4-(carboxymethyl)-L-phenylalanine methyl ester
- 35 N-(Toluene-4-sulfonyl)-L-prolyl-4-(2-methylbenzamido)-L-phenylalanine methyl ester
- N-(Toluene-4-sulfonyl)-L-prolyl-4-(N,N-dimethylaminocarbonylmethyl)-L-phenylalanine
- 40 N-(1-methylimidazol-4-sulfonyl)-L-prolyl-4-hydroxy-L-phenylalanine isopropyl ester

- N-(Toluene-4-sulfonyl)-L-prolyl-4-(2,4,5-trioxo-3-phenyltetrahydroimidazol-1-yl)-L-phenylalanine isopropyl ester
- 5 N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-fluoro-4-hydroxy-L-phenylalanine isopropyl ester
- N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-chloro-4-*t*-butoxy-L-phenylalanine *t*-butyl ester
- 10 N-{N-[(1*S*)-2,10-camphorsultamyl]acetyl}-L-tyrosine *t*-butyl ester
- N-{N-[(1*S*)-2,10-camphorsultamyl]acetyl}-3-chlorotyrosine isopropyl ester
- 15 N-(4-Fluorobenzenesulfonyl)-L-thiaprolyl-4-hydroxy-L-phenylalanine *t*-butyl ester
- N-(Toluene-4-sulfonyl)-L-prolyl-4-(*N,N*-dimethylaminocarbonylmethyl)-L-phenylalanine *t*-butyl ester
- 20 N-(4-Nitrobenzenesulfonyl)-L-prolyl-4-(hydroxy)-L-phenylalanine *t*-butyl ester
- N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-4-hydroxy-L-phenylalanine isopropyl ester
- 25 N-(4-Fluorobenzenesulfonyl)-L-prolyl-4-hydroxy-L-phenylalanine *t*-butyl ester
- N-(pyridin-3-sulfonyl)-L-prolyl-4-hydroxy-L-phenylalanine *t*-butyl ester
- 30 N-(Toluene-4-sulfonyl)-L-prolyl-4-(methanesulfonamido)-L-phenylalanine
- N-(Toluene-4-sulfonyl)-L-prolyl-4-(2,4,5-trioxo-3-(3-chlorophenyl)-tetrahydroimidazol-1-yl)-L-phenylalanine benzyl ester
- 35 N-(1-methylimidazol-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-chloro-4-hydroxy-L-phenylalanine ethyl ester.
- 40 N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl) thiaprolyl-L-3-chloro-4-~~tert~~-butoxy-phenylalanine ~~tert~~-Butyl Ester
- N-[2-(*N*-2,10-camphorsultamyl) acetyl]-L-3-chloro-4-hydroxyphenylalanine Isopropyl Ester

13. A method for binding VLA-4 in a biological sample which method comprises contacting the biological sample with a compound of Claims 1 or 2 under conditions wherein said compound binds to VLA-4.

5 14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of one or more compounds of Claim 1 or 2.

10 15. A method for treating an inflammatory disease in a mammalian patient which disease is mediated by VLA-4 which method comprises administering to said patient a therapeutically effective amount of the pharmaceutical composition of Claim 14.

15 16. The method according to Claim 15 wherein said inflammatory disease is selected from the group consisting of asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetis), inflammatory bowel disease (including ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, and other
20 cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

25 17. The method of claim 14 wherein R¹ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl.

30 18. The method of claim 14 wherein R¹ is selected from the group consisting of 4-methylphenyl, methyl, benzyl, *n*-butyl, 4-chlorophenyl, 1-naphthyl, 2-naphthyl, 4-methoxyphenyl, phenyl, 2,4,6-trimethylphenyl, 2-

(methoxycarbonyl)phenyl, 2-carboxyphenyl, 3,5-dichlorophenyl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl, 3,4-dimethoxyphenyl, 4-(CH₃C(O)NH-)phenyl, 4-trifluoromethoxyphenyl, 4-cyanophenyl, isopropyl, 3,5-di-(trifluoromethyl)phenyl, 4-*t*-butylphenyl, 4-*t*-butoxyphenyl, 4-nitrophenyl, 2-thienyl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl, phenethyl, 1-N-methylimidazol-4-yl, 4-bromophenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-[CH₃SC(=NH)]phenyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methyl-4-pyrazolyl, 2-thiazolyl, 5-methyl-1,3,4-thiadiazol-2-yl, 4-[H₂NC(S)]phenyl, 4-aminophenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,5-difluorophenyl, pyridin-3-yl, pyrimidin-2-yl, 4-(3'-dimethylamino-*n*-propoxy)-phenyl, and 1-methylpyrazol-4-yl.

19. The method of claim 14 wherein R² is selected from the group consisting of hydrogen, methyl, phenyl, benzyl, -(CH₂)₂-2-thienyl, and -
(CH₂)₂-φ.

20. The method of claim 14 wherein R¹ and R² together with the nitrogen atom bound to R² and the SO₂ group bound to R¹ are joined to form a heterocyclic group or substituted heterocyclic group.

21. The method of claim 14 wherein R³ includes all of the isomers arising by substitution with methyl, phenyl, benzyl, diphenylmethyl, -CH₂CH₂-COOH, -CH₂-COOH, 2-amidoethyl, *iso*-butyl, *t*-butyl, -CH₂O-benzyl and hydroxymethyl.

22. The method of claim 14 wherein R² and R³ together with the nitrogen atom bound to R² and the carbon atom bound to R³ form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted, the substituent on said saturated substituted heterocyclic group is not carboxyl.

23. The method of claim 14 wherein Q is -C(O)NH- or -C(S)NH-.

24. The method of claim 14 wherein R⁵ is selected from the group
 5 consisting of *p*-[-OCH(CH₃)φ]benzyl, 4-hydroxybenzyl, 2-carboxybenzyl, 3-carboxybenzyl, 4-carboxybenzyl, 4-(2-carboxyphenoxy)benzyl, 4-(benzyloxy)benzyl, 4-iodobenzyl, 4-methoxybenzyl, 4-nitrobenzyl, 4-(*tert*-butoxy)benzyl, 3,5-diiodo-4-hydroxybenzyl, 4-(benzamido)benzyl, benzyl, 4-hydroxy-3-iodobenzyl, 4-chlorobenzyl, isobutyl, methyl, 4-
 10 (acetamido)benzyl, *n*-butyl, carboxymethyl, 4-aminobutyl, 2-carboxyethyl, 4-(*N,N*-dibenzylamino)benzyl, (*N*-benzylimidazol-4-yl)methyl, 2-thiomethoxyethyl, hydroxymethyl, (*N*-methylimidazol-4-yl)methyl, 4-(isopropyl-C(O)NH-)butyl, 4-(benzamido)butyl, 4-(benzyl-C(O)NH-)butyl, (*N*-methylimidazol-5-yl)methyl, 4-(pyridin-2-yl-C(O)NH-)butyl, 4-(6-methylpyridin-3-yl-C(O)NH-)butyl, 4-(3-methylthien-2-yl-C(O)NH-)butyl,
 15 4-(pyrrol-2-yl-C(O)NH-)butyl, 4-(furan-2-yl-C(O)NH-)butyl, isopropyl, 4-aminobenzyl, 4-(4-phenylbutoxy)benzyl, 4-(1-methylindol-3-yl-C(O)NH-)butyl, 4-(4-methanesulfonylphenyl-C(O)NH-)butyl, 4-(4-acetylphenyl-C(O)NH-)butyl, 4-(4-fluorophenyl-C(O)NH-)butyl, 4-[2-(pyridin-2-yl)ethynyl]benzyl, 4-[2-(3-hydroxyphenyl)ethynyl]benzyl, 4-(pyridin-4-yl-C(O)NH-)benzyl, 4-(pyridin-3-yl-C(O)NH-)benzyl, 4-(3-methylphenyl-NHC(O)NH-)benzyl, 4-(2,3-dihydroindol-2-yl-C(O)NH-)benzyl, 4-(*N,N*-dipentylamino)benzyl, 4-(*N*-pentylamino)benzyl, 4-[2-(*N,N*-dibenzylamino)ethoxy]benzyl, 3-hydroxybenzyl, 4-(*N-n*-butyl-*N-n*-
 25 pentylamino)benzyl, 4-(*N*-4-chlorophenylamino)benzyl, 4-(4-cyanophenyl-NHC(O)NH-)benzyl, 4-(carboxymethoxy)benzyl, 4-(*tert*-butoxycarbonylmethoxy)benzyl, 4-(5-fluoroindol-2-yl-C(O)NH-)benzyl, 4-(1,2,3,4-tetrahydroisoquinolin-3-yl-C(O)NH-)benzyl, 4-(3-methoxyphenyl-NHC(O)NH-)benzyl, 4-[2-(indol-3-yl)ethoxy]benzyl, 4-(4,5-dihydroimidazol-2-ylmethoxy)benzyl, 4-(*n*-propyl-NHC(O)NH-)benzyl, 4-

(N-benzylamino)benzyl, 3-methoxybenzyl, 4-(pyridin-2-yl-C(O)NH-)benzyl,
 4-(N-4-chlorobenzylamino)benzyl, 4-(2-chloromethylsulfonylamino)benzyl,
 4-(N,N-dimethylamino)benzyl, 3-aminobenzyl, 4-(benzyl)benzyl, 2-
 hydroxyethyl, 4-nitrobenzyl, 4-(phenyl-NHC(S)NH-)benzyl, 4-(pyridin-3-yl-
 5 NHC(S)NH-)benzyl, 4-(pyridin-4-ylmethylamino)benzyl, 4-
 [ϕ CH₂OCH₂(Boc-HN)CHC(O)NH-]benzyl, 4-(pyridin-3-yl-C(O)NH-)butyl,
 4-(pyridin-4-yl-C(O)NH-)butyl, 4-(pyridin-3-yl-C(O)NH-)benzyl, 4-
 (pyridin-4-yl-C(O)NH-)benzyl, 4-(N-toluenesulfonylpyrrolidin-2-yl-
 C(O)NH-)butyl, 4-(piperidin-4-yl-C(O)NH-)butyl, 4-(2-Boc-1,2,3,4-
 10 tetrahydroisoquinolin-3-yl-NHCH₂-)benzyl, 4-(2-Boc-1,2,3,4-
 tetrahydroisoquinolin-3-yl-C(O)NH-)benzyl, 4-(pyridin-3-
 ylmethylamino)benzyl, 4-[\mathbf{\phi}CH₂O(O)C(CbzNH)CHCH₂CH₂C(O)NH-
]benzyl, 4-(2-methoxybenzamido)benzyl, 4-(2-bromobenzamido)benzyl, 4-
 (pyrazin-2-yl-C(O)NH-)benzyl, (1-toluenesulfonylimidizol-4-yl)methyl, [1-
 15 (N,N-dimethylaminosulfonyl)imidizol-4-yl]methyl, 4-
 (trifluoromethyl)benzyl, 4-(3,3-dimethylureido)benzyl, 4-
 (methoxycarbonylamino)benzyl, 4-(1,3,3-trimethylureido)benzyl, 4-
 (methoxycarbonyl-N-methylamino)benzyl, 4-cyanobenzyl, 4-(2-formyl-
 1,2,3,4-tetrahydroisoquinolin-3-yl-C(O)NH-)benzyl, phenyl, 4-
 20 (aminomethyl)benzyl, 4-(1-Boc-piperidin-4-yl-C(O)NHCH₂-)benzyl, 4-(1-
 Boc-piperidin-4-yl-C(O)O-)benzyl, 4-(piperidin-4-yl-C(O)NHCH₂-)benzyl,
 4-[(1-methylpiperidin-4-yl)-O-]benzyl, 4-(1,2,3,4-tetrahydroquinolin-2-yl-
 C(O)NH-)benzyl, α -methylbenzyl, 4-(trimethylacetamido)benzyl, 4-(2-
 methylpropionamido)benzyl, 4-(morpholin-4-yl-C(O)NH-)benzyl, 4-(3,3-
 25 diethylureido)benzyl, 4-(2-trifluoromethylbenzamido)benzyl, 4-(2-
 methylbenzamido)benzyl, 4-hydroxy-3-nitrobenzyl, 3-hydroxy-4-(ϕ -
 OC(O)NH-)benzyl, 4-(thiomorpholino-4-yl-C(O)NH-)benzyl, 4-(1,1-
 dioxothiomorpholino-4-yl-C(O)NH-)benzyl, 3-nitro-4-
 (methoxycarbonylmethoxy)benzyl, (2-benzoxazolinon-6-yl)methyl, (2H-1,4-
 30 benzoxazin-3(4H)-one-7-yl)methyl, 4-[N,N-dimethylaminosulfonyl-(N-

methyl)amino]benzyl, 4-[(2-methylpyrrolidin-1-yl)-C(O)NH-]benzyl, (pyridin-4-yl)methyl, 4-(1-methylpiperidin-4-yl-C(O)NH-)benzyl, 4-[bis(*N,N*-dimethylaminothiocarbonyl)amino]benzyl, 4-(*N,N*-dimethylaminosulfonyl)benzyl, 4-(imidazolid-2-one-1-yl)benzyl, 3,4-(ethylenedioxy)benzyl-, 3,4-(methylenedioxy)benzyl- and 4-(3-formylimidazolid-2-one-1-yl)benzyl.

25. The method of claim 14 wherein R^6 is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), methoxy, ethoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, cyclopentoxy, *neo*-pentoxy, 2- α -*iso*-propyl-4- β -methylcyclohexoxy, 2- β -isopropyl-4- β -methylcyclohexoxy, -NH₂, benzyloxy, -NHCH₂COOH, -NHCH₂CH₂COOH, -NH-adamantyl, -NHCH₂CH₂COOCH₂CH₃, -NHSO₂-*p*-CH₃- ϕ , -NHOR⁸ where R⁸ is hydrogen, methyl, *iso*-propyl or benzyl, O-(*N*-succinimidyl), -O-cholest-5-en-3- β -yl, -OCH₂-OC(O)C(CH₃)₃, -O(CH₂)_zNHC(O)W where *z* is 1 or 2 and W is selected from the group consisting of pyrid-3-yl, *N*-methylpyridyl, and *N*-methyl-1,4-dihydro-pyrid-3-yl, and -NR'⁹C(O)-R' where R' is aryl, heteroaryl or heterocyclic and R'' is hydrogen or -CH₂C(O)OCH₂CH₃.

20

26. The method of claim 14 wherein the compound is selected from the group consisting of:

N-(Toluene-4-sulfonyl)-L-prolyl-4-(α -methylbenzyloxy)-L-phenylalanine
N-(Toluene-4-sulfonyl)-L-prolyl-L-tyrosine
N-(Toluene-4-sulfonyl)-L-prolyl-4-carboxyphenylalanine
N-(Toluene-4-sulfonyl)-L-prolyl-3-(carboxy)phenylalanine
N-(Toluene-4-sulfonyl)-L-prolyl-4-(2-carboxyphenoxy)-L-phenylalanine
N-(Toluene-4-sulfonyl)-L-prolyl-O-(benzyl)-L-tyrosine

- N*-(Toluene-4-sulfonyl)-L-prolyl-4-(iodo)-L-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(methoxy)-phenylalanine
- 5 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-nitro-L-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-(*O*-*tert*-butyl)-L-tyrosine
- 10 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(3,5-diiodo)-tyrosine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(aminobenzoyl)-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(3-iodo-4-hydroxy)-phenylalanine
- 15 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-chloro)phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-leucine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-alanine
- 20 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(acetamido)-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-isoleucine
- 25 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-aspartic acid
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-lysine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-glutamic acid
- 30 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-dibenzylamino)-phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(*N*-benzyl)-histidine
- 35 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-dibenzylamino)-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-methionine
- 40 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-serine
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-(*N*-benzyl)-histidine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(1-methyl)histidine

- N*-(Toluene-4-sulfonyl)-L-prolyl-D-(*N*-benzyl)histidine
- N*-(Toluene-4-sulfonyl)-L-glutamyl-L-tyrosine
- 5 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(*N*-3-methyl)histidine
- N*-(Toluene-4-sulfonyl)-L-prolyl- α -amino-2,3-dihydro-(1,4-benzodioxin)-6-propanoic acid
- 10 *N*-(Toluene-4-sulfonyl)-L-prolyl- α -amino-1,3-benzodioxole-5-propanoic acid
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-valine
- 15 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-iodo)-phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(aminobenzoyl)phenylalanine methyl ester
- 20 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-chloro)phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-amino)phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-acetamido)phenylalanine methyl ester
- 25 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-(*N*-benzyl)-histidine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-(3'-tolylureido)-L-phenylalanine
- 30 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-[(2,3,3a,7a-tetrahydro-1H-indole-2-carbonyl)-amino]-L-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-pentylamino)phenylalanine methyl ester
- 35 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-*O*-(2-dibenzylamino-ethyl)-tyrosine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-*O*-[2-(dibenzylamino)ethyl]-tyrosine
- 40 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-pentylamino)phenylalanine

- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(4-chlorobenzylamino)-phenylalanine methyl ester
- 5 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[3-(4-cyanophenyl)-ureido]-phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[3-(4-cyanophenyl)-ureido]-phenylalanine
- 10 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-*O*-(*tert*-butoxycarbonylmethyl)-tyrosine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-*O*-(*tert*-butoxycarbonylmethyl)-tyrosine
- 15 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[(3*S*)-3,4-dihydro-isoquinolin-3-yl-aminocarbonyl]-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-[3-(3-methoxy-phenyl)-ureido]-L-phenylalanine methyl ester
- 20 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-[3-(3-methoxy-phenyl)-ureido]-L-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-*O*-(4,5-dihydro-1*H*-imidazol-2-yl-methyl)-tyrosine
- 25 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(3-propyl-ureido)-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-benzylamino)phenylalanine
- 30 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-benzylamino)phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(4-chlorobenzylamino)-phenylalanine
- 35 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-(4-chloromethanesulfonylamino)-phenylalanine
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-(aminobenzoyl)phenylalanine methyl ester
- 40 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-(benzamido)phenylalanine

- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-tyrosine ethyl ester
- N*-(Toluene-4-Sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-tyrosine
- 5 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[(pyridin-4-yl)methylamino]phenylalanine
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[(pyridin-4-yl)methylamino]phenylalanine methyl ester
- 10 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-(pyridin-3-carboxamido)phenylalanine methyl ester
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-(pyridine-3-carboxamido)phenylalanine
- 15 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-[(pyridin-3-ylmethyl)amino]phenylalanine
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-nitrophenylalanine methyl ester
- 20 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-nitrophenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-methoxybenzamido)phenylalanine ethyl ester
- 25 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-(4-nitro)phenylalanine ethyl ester
- 30 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-bromobenzamido)phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiamorphyl-L-4-aminophenylalanine ethyl ester
- 35 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-acetamidophenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-methoxybenzamido)phenylalanine
- 40 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-acetamidophenylalanine ethyl ester

- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-acetamidophenylalanine
- 5 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-acetamidophenylalanine isopropyl ester
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-L-4-(isonicotinamido)phenylalanine ethyl ester
- 10 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(isonicotinamido)phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(π -toluene-4-sulfonyl)histidine methyl ester
- 15 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-4-(nicotinamido)phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-(*O*-methyl)tyrosine ethyl ester
- 20 *N*-(α -Toluenesulfonyl)-L-prolyl-L-4-(isonicotinamido)phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-bromobenzamido)phenylalanine
- 25 *N*-(α -Toluenesulfonyl)-L-prolyl-L-4-(isonicotinamido)phenylalanine
- N*-(Toluene-4-sulfonyl)-L-(1,1-dioxo)thiamorpholyl-L-4-(2-bromobenzamido))phenylalanine ethyl ester
- 30 *N*-(Toluene-4-sulfonyl)-L-(1,1-dioxo)thiamorpholyl-L-4-(2-bromobenzamido)phenylalanine
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-L-4-(isonicotinamido)phenylalanine
- 35 *N*-(α -Toluenesulfonyl)-L-prolyl-L-4-(2-bromobenzamido)phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-tyrosine isopropyl ester
- 40 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-tyrosine *tert*-butyl ester

- N*-(Toluene-4-sulfonyl)-L-prolyl-L-tyrosine *tert*-butyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-trifluoromethylbenzamido)phenylalanine ethyl ester
- 5 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-methylbenzamido)phenylalanine ethyl ester
- 10 *N*-(Toluene-4-sulfonyl)-L-prolyl-L-4-(2-trifluoromethylbenzamido)phenylalanine
- N*-(4-Fluorobenzenesulfonyl)-L-thiaprolyl-L-tyrosine *tert*-butyl Ester
- 15 *N*-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl)-thiaprolyl-L-tyrosine *tert*-Butyl Ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-(dimethylamino)-L-phenylalanine
- 20 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-[(2-bromo)benzamido]-L-phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-[(pyrazin-2-yl)C(O)NH]-L-phenylalanine methyl ester
- 25 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-(4-nitrobenzoyl)-L-phenylalanine ethyl ester
- N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-4-(2-bromobenzamido)-L-phenylalanine *t*-butyl ester
- 30 *N*-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-4-(2-bromobenzamido)-L-phenylalanine *t*-butyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-4-(1-H-2-oxo-3-methyltetrahydropyrimidin-1-yl)-L-phenylalanine *t*-butyl ester
- 35 *N*-(Toluene-4-sulfonyl)-L-prolyl-4-(1-H-2-oxo-3-methyltetrahydropyrimidin-1-yl)-L-phenylalanine
- 40 *N*-(Toluene-4-sulfonyl)-L-prolyl-3-chloro-4-(*t*-butoxy)-L-phenylalanine *t*-butyl ester
- N*-(Toluene-4-sulfonyl)-L-prolyl-3-chloro-4-(hydroxy)-L-phenylalanine *t*-butyl ester

- N-(Toluene-4-sulfonyl)-L-prolyl-4-(N,N-dimethylureido)-L-phenylalanine t-butyl ester
- 5 N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-chloro-4-(hydroxy)-L-phenylalanine t-butyl ester
- N-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-chloro-4-(hydroxy)-L-phenylalanine isopropyl ester
- 10 N-(Toluene-4-sulfonyl)-L-prolyl-4-(2-methoxyphenyl)-L-phenylalanine t-butyl ester
- N-(Toluene-4-sulfonyl)-L-prolyl-4-(2-methoxyphenyl)-L-phenylalanine
- 15 N-(Toluene-4-sulfonyl)-L-prolyl-[(5-N,N-dimethyl ureido)-pyridin-2-yl]-alanine
- N-(Toluene-4-sulfonyl)-L-prolyl-4-(N,N-dimethylsulfamyl)-L-phenylalanine
- 20 N-(Toluene-4-sulfonyl)-L-prolyl-4-(N¹,N¹,N²-trimethylsulfamyl)-L-phenylalanine
- N-(Toluene-4-sulfonyl)-L-prolyl-(1-t-butoxycarbonylmethylimidazol-4-yl)-L-alanine methyl ester
- 25 N-(Toluene-4-sulfonyl)-L-prolyl-[N,N-dimethylamino carbonylmethylimidazol-4-yl]-L-alanine methyl ester
- N-[4-(dimethyl ureylenyl)-benzenesulfonyl]-L-prolyl-4-hydroxy-L-phenylalanine isopropyl ester
- 30 N-(Toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-chloro-4-hydroxy-L-phenylalanine isopropyl ester
- 35 N-(Toluene-4-sulfonyl)-L-prolyl-3-chloro-4-hydroxy-L-phenylalanine isopropyl ester
- N-(Toluene-4-sulfonyl)-L-prolyl-4-(carboxymethyl)-L-phenylalanine methyl ester
- 40 N-(Toluene-4-sulfonyl)-L-prolyl-4-(2-methylbenzamido)-L-phenylalanine methyl ester

- N-(Toluene-4-sulfonyl)-L-prolyl-4-(N,N-dimethylaminocarbonylmethyl)-L-phenylalanine
- 5 N-(1-methylimidazol-4-sulfonyl)-L-prolyl-4-hydroxy-L-phenylalanine isopropyl ester
- 10 N-(Toluene-4-sulfonyl)-L-prolyl-4-(2,4,5-trioxo-3-phenyltetrahydroimidazol-1-yl)-L-phenylalanine isopropyl ester
- N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-fluoro-4-hydroxy-L-phenylalanine isopropyl ester
- 15 N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-chloro-4-t-butoxy-L-phenylalanine t-butyl ester
- N-{N-[(1S)-2,10-camphorsultamyl]acetyl}-L-tyrosine t-butyl ester
- 20 N-{N-[(1S)-2,10-camphorsultamyl]acetyl}-3-chlorotyrosine isopropyl ester
- N-(4-Fluorobenzenesulfonyl)-L-thiaprolyl-4-hydroxy-L-phenylalanine t-butyl ester
- 25 N-(Toluene-4-sulfonyl)-L-prolyl-4-(N,N-dimethylaminocarbonylmethyl)-L-phenylalanine t-butyl ester
- N-(4-Nitrobenzenesulfonyl)-L-prolyl-4-(hydroxy)-L-phenylalanine t-butyl ester
- 30 N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-4-hydroxy-L-phenylalanine isopropyl ester
- N-(4-Fluorobenzenesulfonyl)-L-prolyl-4-hydroxy-L-phenylalanine t-butyl ester
- 35 N-(pyridin-3-sulfonyl)-L-prolyl-4-hydroxy-L-phenylalanine t-butyl ester
- N-(Toluene-4-sulfonyl)-L-prolyl-4-(methanesulfonamido)-L-phenylalanine
- 40 N-(Toluene-4-sulfonyl)-L-prolyl-4-(2,4,5-trioxo-3-(3-chlorophenyl)-tetrahydroimidazol-1-yl)-L-phenylalanine benzyl ester
- N-(1-methylimidazol-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-3-chloro-4-hydroxy-L-phenylalanine ethyl ester.

N-(4-Fluorobenzenesulfonyl)-L-(5,5-dimethyl) thiaprolyl-L-3-chloro-
4-~~tert~~-butoxy-phenylalanine ~~tert~~-Butyl Ester

5 N-[2-(N-2,10-camphorsultamyl) acetyl]-L-3-chloro-4-hydroxyphenylalanine
Isopropyl Ester

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 98/16070

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/078 A61K38/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 22966 A (BIOGEN INC ; ADAMS STEVEN P (US); LIN KO CHUNG (US); LEE WEN CHERNG) 1 August 1996 see compound BI01013 see page 46, line 32 - page 47, line 35; claims	1,2, 13-17
X	WO 94 07815 A (ABBOTT LAB) 14 April 1994 see page 3, line 5 - line 16; claims; example 105	1
X	EP 0 526 348 A (SANOFI ELF) 3 February 1993 see claims; examples 33,62,66,69	1,2

-/--

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document member of the same patent family

Date of the actual completion of the international search

23 December 1998

Date of mailing of the international search report

14/01/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5918 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Fuhr, C

INTERNATIONAL SEARCH REPORT

Inter. Appl. No.
PCT/US 98/16070

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 12181 A (MERCK & CO INC ; EGBERTSON MELISSA S (US); TURCHI LAURA M (US); HAR) 9 June 1994 see claims; example 31 ---	1,2
X	CHEMICAL ABSTRACTS, vol. 125, no. 3, 15 July 1996 Columbus, Ohio, US; abstract no. 34164, INOE, TOSHIHISA ET AL: "Preparation of amino acid esters and detection of leukocyte, esterase, or protease" XP002087653 see abstract -& JP 08 073422 A (KYOTO DAIICHI KAGAKU KK, JAPAN) see page 6 ---	1
A	WO 95 15973 A (CYTEL CORP) 15 June 1995 see page 8, line 16 - line 26; claims; examples ---	1,2, 13-17
X	CHEMICAL ABSTRACTS, vol. 108, no. 19, 9 May 1988 Columbus, Ohio, US; abstract no. 167952, EL-NAGGAR, A. M. ET AL: "Synthesis and antimicrobial activity of some new N-coumarin-6-sulfonyl amino acid and dipeptide derivatives" XP002086188 see compound having RN: 113789-72-3 see abstract & AFINIDAD (1987), 44(411), 431-3 CODEN: AFINAE; ISSN: 0001-9704, 1987, ---	2,3
X	CHEMICAL ABSTRACTS, vol. 99, no. 21, 21 November 1983 Columbus, Ohio, US; abstract no. 176262, EL-NAGGAR, A. M. ET AL: "Synthesis and biological activity of some new quinoline-8- sulfonylamino acid and dipeptide derivatives" XP002086190 see compound having RN: 87650-85-9 see abstract & ACTA PHARM. JUGOSL. (1983), 33(2), 103-10 CODEN: APJUA8; ISSN: 0001-6667, 1983, ---	2,3
	-/-	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/16070

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CHEMICAL ABSTRACTS, vol. 106, no. 25, 22 June 1987 Columbus, Ohio, US; abstract no. 210288, RESHETOVA, O. S. ET AL: "Analysis of N-dansyl peptide methyl esters by means high performance liquid chromatography and mass spectrometry" XP002086189 see compound having RN: 108375-98-0 see abstract & BIOORG. KHIM. (1987), 13(3), 320-37 CODEN: BIKHD7,1987,</p>	2,3
X	<p>EL-NAGGAR, A. M ET AL: "Synthesis and biological activity of some new dibenzofuran- and 7-nitrodibenzofuran-2-sulfonyl amino acid derivatives" ACTA PHARM. JUGOSL. (1985), 35(1), 15-22 CODEN: APJUA8;ISSN: 0001-6667,1985, XP002051689 see compound XXVIII see table 1</p>	2,3
X	<p>SIMANIS, VIESTURS ET AL: "Recognition and utilization of dansyl-dipeptides in manual dansyl-Edman sequencing" INT. J. PEPT. PROTEIN RES. (1982), 19(1), 67-70 CODEN: IJPPC3;ISSN: 0367-8377,1982, XP002086186 see figure 1</p>	1,3
X	<p>JP 04 154732 A (NIPPON KAYAKU CO LTD) 27 May 1992 see page 191, left-hand column; table</p>	1,3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/16070

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 15-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 98/16070

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9622966	A	01-08-1996	AU 4911596 A BG 101841 A BR 9606778 A CA 2211181 A CN 1177343 A CZ 9702340 A EP 0805796 A FI 973087 A HU 9702461 A NO 973384 A PL 321848 A SK 98797 A	14-08-1996 30-04-1998 06-01-1998 01-08-1996 25-03-1998 18-03-1998 12-11-1997 22-09-1997 28-04-1998 19-09-1997 22-12-1997 04-02-1998
WO 9407815	A	14-04-1994	NONE	
EP 0526348	A	03-02-1993	FR 2679903 A AT 163289 T AU 691223 B AU 1154195 A AU 658664 B AU 2475892 A BR 9205336 A CA 2093221 A,C CA 2206776 A CZ 9300682 A DE 69224450 D DE 69224450 T ES 2117038 T FI 931476 A FI 980175 A WO 9303013 A HU 68927 A HU 9500474 A IL 102703 A JP 2633085 B JP 6501960 T LT 114 A,B LV 10091 A,B MX 9204487 A NO 180047 B NZ 243795 A SG 47501 A SK 42693 A US 5397801 A US 5481005 A US 5578633 A US 5338755 A ZA 9205781 A	05-02-1993 15-03-1998 14-05-1998 04-05-1995 27-04-1995 02-03-1993 16-11-1993 03-02-1993 03-02-1993 19-01-1994 26-03-1998 30-07-1998 01-08-1998 01-04-1993 27-01-1998 18-02-1993 28-08-1995 30-10-1995 18-03-1997 23-07-1997 03-03-1994 15-06-1994 10-05-1994 01-02-1993 28-10-1996 27-04-1995 17-04-1998 06-10-1993 14-03-1995 02-01-1996 26-11-1996 16-08-1994 02-03-1993
WO 9412181	A	09-06-1994	AU 675689 B AU 5826894 A CA 2150550 A EP 0673247 A JP 8504194 T US 5648368 A	13-02-1997 22-06-1994 09-06-1994 27-09-1995 07-05-1996 15-07-1997
WO 9515973	A	15-06-1995	AU 693143 B AU 1215695 A	25-06-1998 27-06-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/16070

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9515973 A		CA 2177840 A	15-06-1995
		CN 1142832 A	12-02-1997
		EP 0737204 A	16-10-1996
		JP 9509146 T	16-09-1997
		NZ 277206 A	24-11-1997
		US 5688913 A	18-11-1997
		US 5821231 A	13-10-1998
		US 5770573 A	23-06-1998
JP 04154732 A	27-05-1992	NONE	

This Page Blank (uspto)